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(57) Abstract

1-(4-aminophenyl)pyrazoles optionally substituted on the 3- and 5-positions of the pyrazole ring and on the amino group at the 4-position of the phenyl ring are disclosed and described, which pyrazoles inhibit IL-2 production in T-lymphocytes.

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SUBSTITUTED 1-(4-AMINOPHENYL)PYRAZOLES AND THEIR USE AS ANTI-INFLAMMATORY AGENTS

Background of the Invention

It has been well established that T-cells play an important role in regulating immune response (F. Powrie and R.L. Coffman, Immunol. Today, 14, p. 270 (1993)). Indeed, activation of T-cells is often the initiating event in many inflammatory and autoimmune diseases. IL-2 is an autocrine growth factor which plays an essential role in the regulation of T-cell activation and proliferation. Clinical studies have shown that interference with IL-2 activity effectively suppresses immune response *in vivo* (T.A. Waldmann, Immunol. Today, 14, 270 (1993)). Accordingly, agents which inhibit IL-2 production are therapeutically useful for selectively suppressing immune response in a patient in need of such immunosuppression.

Previously, others have attempted to interfere with the activity of IL-2 by using cytokine antagonists, monoclonal antibodies, toxins and other biologics which seek to prevent IL-2 from binding to its receptor (G. Mazur and I. Frydecka, Acta Haematol. Pol., 24(4), p. 307 (1993)). More recently, others have attempted to inhibit IL-2 production at the T cell level, for example by blocking the expression of IL-2 mRNA with glucocorticoids or cyclosporin A. However, to date, the reported compounds suffer from several disadvantages such as low potency, poor *in vivo* activity, toxicity and poor oral bioavailability. Accordingly, a need exists for compounds that can effectively inhibit IL-2 production for preventing and treating immune disorders.

A number of 3,5-disubstituted-1-(4-substituted)phenypyrazoles are available commercially or are known in the literature. These include N-{4-[3,5-bis(trifluoromethyl)pyrazol-1-yl]phenyl}-4-chlorobenzamide, N-{4-[3,5-bis(trifluoromethyl)pyrazol-1-yl]phenyl}-4-trifluoromethyoxybenzamide, N-{4-[3,5-bis(trifluoromethyl)pyrazol-1-yl]phenyl}-3,5-dimethylisoxazole-4-carboxamide, N-{4-[3,5-bis(trifluoromethyl)pyrazol-1-yl]phenyl}-4-methyl-1,2,3-thiadiazole-5-carboxamide, N-{4-[3,5-bis(trifluoromethyl)pyrazol-1-

yl]phenyl}-N'-(3,5-dichlorophenyl)urea. N-{4-[3,5-bis(trifluoromethyl)pyrazol-1-yl]phenyl}-N'-(3,5-difluorophenyl)urea, and N-{4-[3,5-bis(trifluoromethyl)pyrazol-1-yl]phenyl}-N'-*n*-propylurea which are available commercially as chemical intermediates from Maybridge Chemical Company Ltd., Trevillett, Tintagel, Cornwall PL34 OHW, UK.

N-[4-(3,5-dimethylpyrazol-1-yl)phenyl]acetamide (Bouchet and Coquelet, Bull. Soc. Chim. Fr. 1976, 195), N-[4-(3-methyl-5-chloropyrazol-1-yl)phenyl]acetamide (Michaelis and Behn, Chem. Ber. 1900, 33, 2602), N-[4-(3-methyl-5-(methylthio)pyrazol-1-yl)phenyl]acetamide (Michaelis, Justus Liebigs Ann. Chem., 1911, 378, 346), N-[4-(3-methyl-5-phenylpyrazol-1-yl)phenyl]benzamide (Barry et al., J. Chem. Soc. 1956, 4974), N-[4-(3-methyl-5-ethoxypyrazol-1-yl)phenyl]acetamide (Hoechster Farbw., DE 92990), N-[4-(3,5-dimethylpyrazol-1-yl)phenyl]-4-methoxybenzylamine, N-[4-(3,5-dimethylpyrazol-1-yl)phenyl]-4-nitrobenzylamine (Fernandes et al. J. Indian Chem. Soc. 1977, 54, 923), 4-(3,5-dimethylpyrazol-1-yl)-N-methylbenzamide (Wright et al., J. Med. Chem. 1964, 7, 102), 4-methoxy- and 4-nitro-alpha-{[4-(3,5-dimethylpyrazol-1-yl)phenyl]amino}benzeneacetonitrile and N-[4-(3,5-dimethylpyrazol-1-yl)phenyl]-4-methoxy-(and 4-nitro)-benzenemethaneamine (Fernandes et al., J. Indian Chem. Soc. 1977, 54, 923) are described in the chemical or patent literature. In no case is antiinflammatory activity or ability to inhibit IL-2 production associated with or described for any of these compounds.

1-(4-Methylaminophenyl)-5-(4-methylsulfonylphenyl)-3-trifluoromethylpyrazole, 1-(4-methylaminophenyl)-5-(4-methylsulfonylphenyl)-3-difluoromethylpyrazole (K. Tsuji et al., Chem. Pharm. Bull., 1997, 45, 1475) and 3-cyano-1-(4-methylaminophenyl)-5-(4-methylsulfonylphenyl)pyrazole and 3-cyano-1-(4-ethylaminophenyl)-5-(4-methylsulfonylphenyl)pyrazole (K. Tsuji et al., Chem Pharm. Bull. 1997, 45, 987) are among several compounds described as having antiinflammatory activity due to their ability to inhibit an isoform of cyclooxygenase referred to as COX-2. In neither case is the inhibition of IL-2 production mentioned.

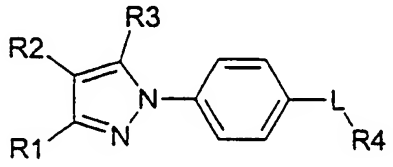
Among a series of substituted pyrazoles having antiinflammatory activity described by M. Matsuo (EP 418845 A1) are 1-[4-(C_1-C_6 alkylamino)phenyl]- and [4-(C_1-C_6 acylamino)phenyl]pyrazoles substituted on the pyrazole on either the 3-,4-, or 5-position with

CF_3, halogen, dimethylaminomethyl, CN, C_{1-6} alkylthio, or esterified carboxy and on another of the 3-, 4-, or 5-positions with a substituted aryl or heteroaryl ring. No mention is made of inhibition of IL-2 production.

BRIEF SUMMARY OF THE INVENTION

The compounds of this invention are 1-(4-aminophenyl)pyrazoles optionally substituted on the 3- and 5-positions of the pyrazole ring and on the amino group on the 4-position of the phenyl ring having antiinflammatory activity by virtue of their ability to inhibit IL-2 production in T-lymphocytes.

In its broadest generic aspect, the invention comprises 1-(4-aminophenyl)pyrazoles of Formula I



Formula I

wherein:

R_1 and R_3 are the same or different and each is CF_3, halogen, CN, C_{1-8} alkyl or branched alkyl or C_{1-8} alkenyl or branched alkenyl or C_{3-8} cycloalkyl optionally substituted with OH, CN or methoxy; C_{1-8} alkoxy, C_{1-4} alkyloxyalkyl, C_{1-8} alkylthio, C_{1-4} alkylthioalkyl, C_{1-8} dialkylamino, C_{1-4} dialkylaminoalkyl, CO_2R_5 where R_5 is C_{1-4} alkyl or C_{1-4} alkenyl optionally substituted with carbocyclyl or heterocyclyl; aryl or heterocyclyl connected to the pyrazole in any position that makes a stable bond, optionally substituted with halogen, C_{1-4} alkyl, C_{1-4} alkenyl, CN, Me_2N, CO_2Me, OMe, aryl, heterocyclyl or R_5.

R_2 is H, halogen, or methyl.

L is -NHC(O)-, -NHC(O)O-, -NHC(O)C(O)-, -NHC(S)-, -NH-, -NHC(O)NH, NHC(S)NH, $NHCH_2$, -NHCH(R_6)- , where R_6 is H, CN, C_{1-6} alkyl, C_{1-6} alkyloxyoalkyl C_{1-6} alkythioalkyl, C_{1-6} alkylsulfinylalkyl, C_{1-6} alkysulfonylalkyl, C_{3-6} cycloalkyl, or heterocyclyl or aryl optionally substituted with a halogen, C_{1-4} alkyl, CN, Me_2N, CO_2Me or OMe, or -NHC(R_6)-lower alkyl.

R_4 is C_{1-8} alkyl, C_{1-8} alkyloxy, C_{1-8} alkylthio, C_{1-8} alkylamino, C_{1-4} alkoxyalkyl, C_{1-4} alkylthioalkyl, C_{1-4} alkylaminoalkyl C_{1-4} dialkylalkylaminoalkyl, carbocyclyl or heterocyclyl, optionally substituted with one or more halogen, -CN, $-NO_2$; SO_2NH_2, or R_7 where R_7 is phenyl, heterocyclyl, C_{3-6} cycloalkyl, C_{1-6} alkyl, C_{2-6} alkenyl, C_{1-6} alkyloxyalkyl, C_{1-6} alkylthioalkyl, C_{1-6} alkylsulfinylalkyl, C_{1-6} alkylsulfonylalkyl or C_{2-6} alkynyl, optionally substituted with halogen, OH, alkyloxy, CN, COO-lower alkyl, -CONH-lower alkyl, -CON(lower alkyl)$_2$, dialkylamino, phenyl or heterocyclyl; CO_2R_7, -N(R_7)$_2$, -NH(R_7), -C(O)R_7, -OR^7, S(O)$_n$$R_7$ where n is 0, 1 or 2, -SO_2NHR_7, -$SO_2N(R_7)_2$.

Detailed Description of the Invention

In order that the invention herein described may be more fully understood, the following detailed description is set forth. As used herein, the following abbreviations are used:

BOC or t-BOC is tertiary butoxycarbonyl

DMAP is 4-dimethylamino pyridine

Bu is butyl

DIBAL is diisobutylaluminum hydride

DMF is dimethylformamide

Et is ethyl

Me is methyl

Oxz is oxazole

Ph is phenyl

Pr is propyl

Py is pyridine

PyBOP is Benzotriazole-1-yl-oxy-tris-pyrrolidino-phosphonium hexafluorophosphate

Th is thiophene

THF is tetrahydrofuran

Thz is thiazole

Rt is room temperature

EDC is 1-(3-dimethylaminopropyl)-3-ethylcarbodimide hydrochloride.

Also, as used herein, each of the following terms, used alone or in conjunction with other terms, are defined as follows (except where noted to the contrary):

The term "alkyl" refers to a saturated aliphatic radical containing from one to ten carbon atoms. "Alkyl" refers to both branched and unbranched alkyl groups. Preferred alkyl groups are straight chain alkyl groups containing from one to eight carbon atoms and branched alkyl groups containing from three to eight carbon atoms. More preferred alkyl groups are straight chain alkyl groups containing from one to six carbon atoms and branched alkyl groups containing from three to six carbon atoms. "Alkyl", as used herein, includes unsubstituted alkyl radicals, those radicals that are partially or fully halogenated and those radicals substituted with one to four, preferably one or two, substituents selected from amino, cyano, nitro, methoxy, ethoxy and hydroxy. The term "cycloalkyl" refers to the cyclic analog of an alkyl group, as defined above. Preferred cycloalkyl groups are saturated cycloalkyl groups containing from three to eight carbon atoms, and more preferably three to six carbon atoms. "Alkyl" and "cycloalkyl", as used herein, include unsubstituted alkyl and cycloalkyl radicals, those radicals that are partially or fully halogenated and those radicals substituted with one to four, preferably one or two, substituents selected from halo, amino, cyano, nitro, methoxy, ethoxy and hydroxy. It should be understood that any combination term using an "alk" or "alkyl" prefix refers to analogs according to the above definition of "alkyl". For example, terms such as "alkoxy", "alkythio" refer to alkyl groups linked to a second group via an oxygen or sulfur atom.

The terms "alkenyl" and "alkynyl" refer to a mono- or polyunsaturated aliphatic hydrocarbon radical containing from two to twelve carbon atoms, containing at least one double or triple bond, respectively. "Alkenyl" and "alkynyl" refer to both ranched and unbranched alkenyl and alkynyl groups. Preferred alkenyl and alkynyl groups are straight chain alkenyl or

alkynyl groups containing from two to eight carbon atoms and branched alkenyl or alkynyl groups containing from five to ten carbon atoms. More preferred alkenyl and alkynyl groups are straight chain alkenyl or alkynyl groups containing from two to six carbon atoms and branched alkenyl or alkynyl groups containing from five to eight carbon atoms. The term "cycloalkenyl" refers to the cyclic analog of an alkenyl group, as defined above. Preferred cycloalkenyls include cycloalkenyl rings containing from three to eight carbon atoms, and more preferably, from three to six carbon atoms. "Alkenyl", "alkynyl" and "cycloalkenyl", as used herein, include unsubstituted alkenyl or alkynyl radicals, those radicals that are partially or fully halogenated and those radicals substituted with one to four, preferably one or two, substituents selected from halo, amino, cyano, nitro, methoxy, ethoxy and hydroxy.

The term "aryl" refers to phenyl and naphthyl, phenyl and naphthyl that are partially or fully halogenated and phenyl and naphthyl substituted with halo, alkyl, hydroxyl, nitro, -COOH, -CO(lower alkoxy), -CO(lower alkyl), amino, alkylamino, dialkylamino, alkoxy, -NCOH, -NCO(lower alkyl), $-NSO_2$-Ph(halo)$_{0-3}$, Ph, -O-Ph; naphthyl, -O-naphthyl, pyrrolyl, pyrrolyl substituted with lower alkyl, pyridyl, pyridinyl, pyrazinyl, pyrimidinyl and pyridazinyl.

The term "carboxy alkyl" refers to an alkyl radical containing a –COOH substituent.

The term "halo" refers to a halogen radical selected from fluoro, chloro, bromo or iodo. Preferred halo groups are fluoro, chloro and bromo.

The term "carbocyclyl" refers to a stable 3-8 membered (but preferably, 5 or 6 membered) monocyclic or 7-11 membered bicyclic radical which may be either saturated or unsaturated, aromatic or non-aromatic. Preferred carbocycles include, for example, phenyl, naphthyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclopentenyl, cyclohexenyl, cycloheptenyl, indanyl, indenyl, dihydronaphthyl and tetrahydronaphthyl. Most preferred heterocycles of this invention are phenyl, naphthyl, cyclohexyl, tetrahydronaphthyl and indanyl. "Carbocyclyl" refers to unsubstituted carbocyclic radicals, those radicals that are partially or fully halogenated and those radicals substituted with alkyl; hydroxyl; nitro; -COOH; -CO(lower alkoxy); -CO(lower alkyl); amino; alkylamino; dialkylamino; alkoxy; -

NCHO; -NCO(lower alkyl); -NSO_2-Ph(halo)$_{0-3}$, Ph; -O-Ph; naphthyl; -O-naphthyl; pyrrolyl; pyrrolyl substituted with lower alkyl; pyridyl; pyridinyl; pyrazinyl; pyrimidinyl and pyridazinyl

The term "heterocycle" refers to a stable 5-8 membered (but preferably, 5 or 6 membered) monocyclic or 8-11 membered bicyclic heterocycle radical which may be either saturated or unsaturated, aromatic or non-aromatic, and which may be optionally benzo- or pyridofused if monocyclic. Each heterocycle consists of carbon atoms and from 1 to 4 heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur. As used herein, "nitrogen" and "sulfur" include any oxidized form of nitrogen and sulfur and the quaternized form of any basic nitrogen. The heterocycle may be attached by any atom of the cycle, which results in the creation of a stable structure. Preferred heterocycles include, for example, benzimidazolyl, furyl; imidazolyl, imidazolinyl, imidazolidinyl, quinolinyl, isoquinolinyl, indolyl, oxazolyl, pyridyl, pyrrolyl, pyrrolinyl, pyrazolyl, pyrazinyl, pyrimidinyl, pyridazinyl, quinoxolyl, piperidinyl, morpholinyl, thiomorpholinyl, furyl, thienyl, triazolyl, thiazolyl, β-carbolinyl, tetrazolyl, thiazolidinyl, benzofuranoyl, thiamorpholinyl sulfone, benzoxazolyl, oxopiperidinyl, oxopyrroldinyl, oxoazepinyl, azepinyl, isoxazolyl, tetrahydropyranyl, tetrahydrofuranyl, thiadiazoyl, benzodioxolyl, tetrahydrothiophenyl and sulfolanyl. Most preferred heterocycles of this invention include imidazolyl, pyridyl, pyrrolyl, pyrazolyl, piperidinyl, morpholinyl, furyl, thienyl, thiazolyl and the benzo- and pyrido-fused derivatives thereof. "Heterocyclyl" refers to unsubstituted heterocycle radicals, those radicals that are partially or fully halogenated and those radicals substituted with alkyl; hydroxyl; nitro; -COOH; -CO(lower alkoxy); -CO(lower alkyl); amino; alkylamino; dialkylamino; alkoxy; -NCHO; -NCO(lower alkyl); -NSO_2-Ph(halo)$_{0-3}$, Ph; -O-Ph; naphthyl; -O-naphthyl; pyrrolyl; pyrrolyl substituted with lower alkyl; pyridyl; pyridinyl; pyrazinyl; pyrimidinyl and pyridazinyl.

The term "lower" used in conjunction with other terms (e.g., "alkyl", "alkoxy" and the like) refers to a radical containing from one to six, preferably from one to five and more preferably, from one to four carbon atoms. For example, a "lower alkyl" group is a branched or unbranched alkyl radical containing from one to six carbon atoms.

The term "patient" refers to a warm-blooded animal, and preferably a human.

The term "prevention" or "prophylaxis" refers to a measurable reduction in the likelihood of a patient acquiring a disease or disorder.

The term "treatment" refers to either the alleviation of the physical symptoms of a disease or an improvement in the physiological markers used to measure progression of a disease state.

The term "pharmaceutically acceptable carrier" or "pharmaceutically acceptable adjuvant" refers to a non-toxic carrier or adjuvant that may be administered to a patient together with a compound of this invention and which does not destroy the pharmacological activity of that compound.

The term "pharmaceutically effective amount" refers to an amount effective in suppressing the immunity of a patient in need of such treatment. Suppressed immunity can be readily measured by observing the degree of inhibition of IL-2 production in human T-cells (PBLs) by known techniques.

The term "prophylactically effective amount" refers to an amount effective in preventing or reducing the likelihood of initial onset or progression of an immune disorder in a patient susceptible to such disorder.

It should be understood that any compounds of this invention containing one or more asymmetric carbon atoms may occur as racemates and racemic mixtures, single enantiomers, diastereomeric mixtures and individual diastereomers. All such isomeric forms of these compounds are expressly included in the present invention. Each stereogenic center may be in the R or S configuration, or a combination of configurations.

The compounds of this invention are defined to include pharmaceutically acceptable derivatives thereof. A "pharmaceutically acceptable derivative" refers to any pharmaceutically acceptable salt, ester, or salt of an ester of a compound of this invention, or any other compound which, upon administration to a patient, is capable of providing (directly

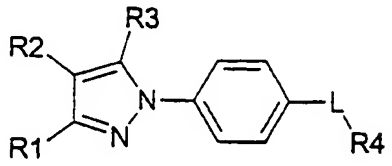
or indirectly) a compound of this invention, a pharmacologically active metabolite or pharmacologically active residue thereof.

Combinations of substituents and variables encompassed by this invention are only those that result in the formation of stable compounds. The term "stable" as used herein, refers to compounds which possess stability sufficient to permit manufacture and administration to a patient by conventional methods known in the art. Typically, such compounds are stable at a temperature of 40°C or less, in the absence of moisture or other chemically reactive conditions, for at least a week.

The compounds of this invention may be used in the form of salts derived from inorganic or organic acids. Included among such acid salts, for example, are the following: acetate, adipate, alginate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, citrate, camphorate, camphorsulfonate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, fumarate, glucoheptanoate, glycerophosphate, hemisulfate, heptanoate, hexanoate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethanesulfonate, lactate, maleate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, oxalate, pectinate, persulfate, 3-phenylpropionate, picrate, pivalate, propionate, succinate, tartrate, tosylate and undecanoate.

This invention relates to substituted 1-(4-aminophenyl)pyrazoles and analogs thereof that inhibit interleukin-2 (IL-2) production. In one embodiment, this invention relates to a novel class of substituted 1-(4-aminophenyl)pyrazoles and pharmaceutical compositions comprising these compounds. This invention also relates to methods for producing such novel substituted 1-(4-aminophenyl)pyrazoles. Because of their selective immunomodulating properties, the compounds and pharmaceutical compositions of this invention are particularly well suited for preventing and treating immune disorders, including autoimmune disease, inflammatory disease, organ transplant rejection and other disorders associated with IL-2 mediated immune response.

The substituted 1-(4-aminophenyl)pyrazoles of this invention are represented by Formula I



Formula I

wherein:

R_1 and R_3 are the same or different and each is CF_3, halogen, CN, C_{1-8} alkyl or branched alkyl or C_{1-8} alkenyl or branched alkenyl or C_{3-8} cycloalkyl optionally substituted with OH, CN or methoxy; C_{1-8} alkoxy, C_{1-4} alkyloxyalkyl, C_{1-8} alkylthio, C_{1-4} alkylthioalkyl, C_{1-8} dialkylamino, C_{1-4} dialkylaminoalkyl, CO_2R_5 where R_5 is C_{1-4} alkyl or C_{1-4} alkenyl optionally substituted with carbocyclyl or heterocyclyl; aryl or heterocyclyl connected to the pyrazole in any position that makes a stable bond. optionally substituted with halogen, C_{1-4} alkyl, C_{1-4} alkenyl, CN, Me_2N, CO_2Me, OMe, aryl, heterocyclyl or R_5.

R_2 is H, halogen or methyl.

L is -NHC(O)-, -NHC(O)O-, -NHC(O)C(O)-, -NHC(S)-, -NH-, -NHC(O)NH, NHC(S)NH, $NHCH_2$, -NHCH(R_6)- , where R_5 is H, CN, C_{1-6} alkyl, C_{1-6} alkyloxyoalkyl C_{1-6} alkythioalkyl, C_{1-6} alkylsulfinylalkyl, C_{1-6} alkysulfonylalkyl, C_{3-6} cycloalkyl, or heterocyclyl or aryl optionally substituted with a halogen, C_{1-4} alkyl, CN, Me_2N, CO_2Me or OMe, or -NHC(R_6)-lower alkyl.

R_4 is C_{1-8} alkyl, C_{1-8} alkyloxy, C_{1-8} alkylthio, C_{1-8} alkylamino, C_{1-4} alkoxyalkyl, C_{1-4} alkylthioalkyl, C_{1-4} alkylaminoalkyl, C_{1-4} dialkylalkylaminoalkyl, carbocyclyl or heterocyclyl, optionally substituted with one or more halogen, -CN, $-NO_2$, SO_2NH_2, or R_7 where R_7 is phenyl, heterocyclyl, C_{3-6} cycloalkyl, C_{1-6} alkyl, C_{2-6} alkenyl, C_{1-6} alkyloxyalkyl, C_{1-6} alkylthioalkyl, C_{1-6} alkylsulfinylalkyl, C_{1-6} alkylsulfonylalkyl or C_{2-6} alkynyl, optionally

substituted with halogen, OH, alkyloxy, CN, COO-lower alkyl, -CONH-lower alkyl, -CON(lower alkyl)$_2$, dialkylamino, phenyl or heterocylcyl; CO_2R_7, -$N(R_7)_2$, -$NH(R_7)$, -$C(O)R_7$, -OR^7, $S(O)_nR_7$ where n is 0, 1 or 2, -SO_2NHR_7, -$SO_2N(R_7)_2$.

Preferably, the novel substituted 1-(4-aminophenyl)pyrazoles of Formula I are those wherein:

R_1 is straight-chained, branched or cyclo- C_{3-8} alkyl, alkenyl, or alkynyl; C_{1-3} alkyloxyalkyl, C_{1-5} alkyloxy, C_{1-3}alkylthioalkyl, C_{1-5} alkylthio, CF_3; heterocyclyl or aryl optionally substituted with halogen, C_{1-4} alkyl, CN, alkoxy or Me_2N;

R_2 is H; and

R_3 is halogen, Me, Et, CF_3, CN, cyclopropyl, vinyl, SMe, OMe, heterocyclyl or aryl optionally substituted with halogen, C_{1-4} alkyl, CN, alkoxy or Me_2N;

L is -NHC(O)-, -NH-, -NHC(O)NH, -C(O)NH, or -NHCH(R_6)-, where R_6 is H, C_{1-4} alkyl, or CN and

R_4 is C_{1-6} alkyl, C_{1-4} alkyloxyalkyl, C_{1-4} alkylthioalkyl, cyclohexyl, cyclopentyl, indanyl, indolyl, phenyl, thienyl, naphthyl, isoxazolyl or pyridyl, optionally substituted with one or more halogen, -CN, -NO_2, SO_2NH_2, or R_7 where R_7 C_{1-6} alkyl, C_{2-6} alkenyl, C_{1-6} alkyloxyalkyl, C_{1-6} alkylthioalkyl, or C_{2-6} alkynyl, optionally substituted with OH, CN, -COO-lower alkyl, -CONH-lower alkyl, -CON(lower alkyl)$_2$, dialkylamino, or heterocylcyl; CO_2R_7, -$N(R_7)_2$, -$NH(R_7)$, -$C(O)R_7$, -OR_7, $S(O)_nR_7$ where n is 0, 1 or 2, -SO_2NHR_7, -$SO_2N(R_7)_2$.

More preferred are novel substituted 1-(4-aminophenyl)pyrazoles of Formula I wherein:

R_1 is Et, *i*-Pr, *t*-Bu, cyclopentyl, CF_3, -OEt, $MeOCH_2$-, 2- or 3-tetrahydrofuranyl, 2-, 3-, or 4-pyridyl or 2-pyrazinyl;

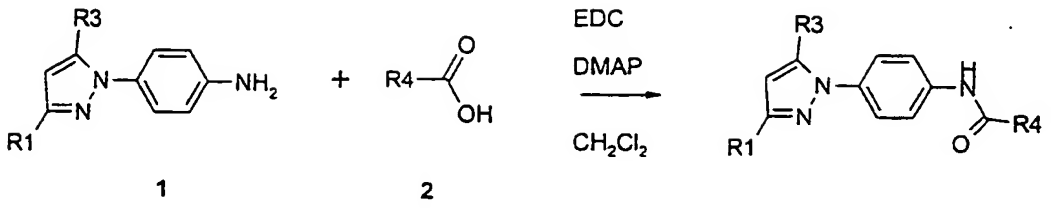
R_2 is H;

R_3 is Halogen, CN, CF_3, Me, 5Me or Et;

L is –NHC(O)-, -NH- or $-NHCH_2-$; and

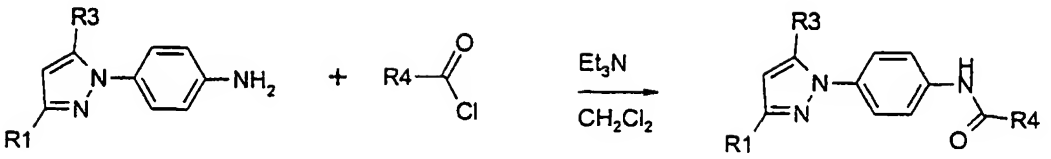
R_4 is alkyl, cyclohexyl, cyclopentyl, indanyl, indolyl, phenyl, thienyl, naphthyl, or pyridyl, optionally substituted with one or more halogen, -CN, or R_7 where R_7 C_{1-6} alkyl, C_{2-6} alkenyl, C_{1-6} alkyloxyalkyl, C_{1-6} alkylthioalkyl, optionally substituted with OH, CN, or heterocylcyl; $-CO_2R_7$, $-N(R_7)_2$, $-NH(R_7)$, $-C(O)R_7$, or $-OR_7$.

Compounds of Formula I in which L is -NHC(O)- may be prepared by one of the methods outlined below. For example, a (4-aminophenyl)-3,5-disubstituted pyrazole 1 may be reacted with a carboxylic acid 2 under suitable coupling conditions known to one skilled in the art, for example EDC and a base catalyst such as N,N-dimethylaminopyridine in a suitable solvent such as methylene chloride acetonitrile or DMF (Method A). Alternatively, 1 could be coupled with an acid halide 3 in the presence of a suitable base such as triethylamine in a suitable solvent such as methylene chloride (Method B). In another alternative method, these compounds could be prepared by reacting a 4-(acetamido)phenylhydrazine 4 with a 1,5-disubstituted-2,4-pentanedione 5 in a suitable solvent such as acetic acid (Method C). If R_1 is different from R_3, then two different products may form using Method C, which may be separated by techniques such as chromatography known to those skilled in the art.



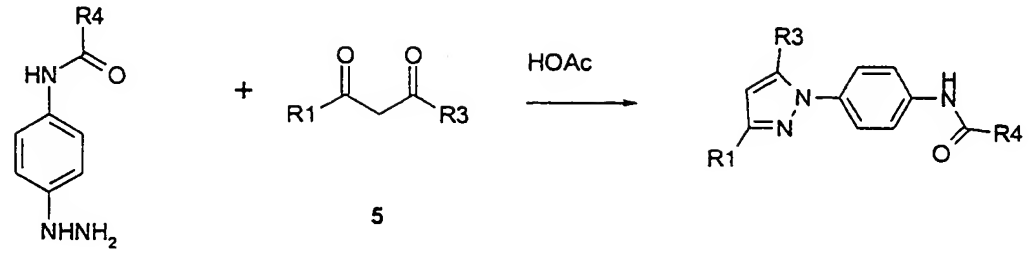
1 2

Method B



1 3

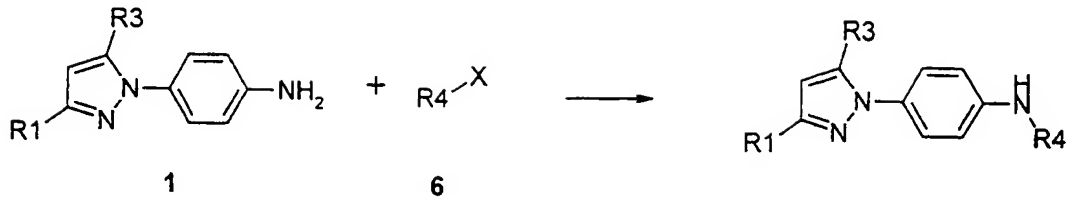
Method C



4 5

Compounds of Formula I in which L is -NH- and R_4 is a heteroaryl ring may be prepared, as illustrated below, by reaction of a (4-aminophenyl)-3,5-disubstituted pyrazole 1 with a heterocycle 6 containing a labile substituent such as a halogen, which may be displaced by nucleophilic substitution (Method D). The reaction may be carried out in a sealed tube or an open vessel, at ambient temperature or heated to 150°C in a suitable solvent such as dioxane or THF. A base such as sodium bis-trimethylsilyl amide may be added to the reaction.

Method D

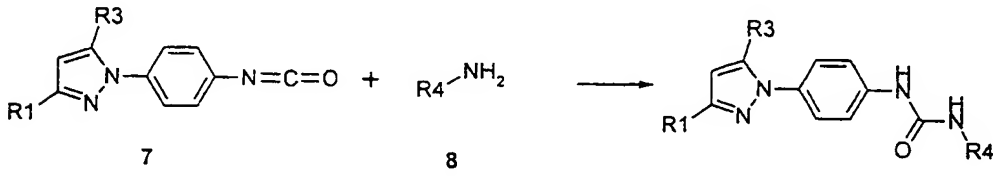


1 6

X is halogen or other leaving group

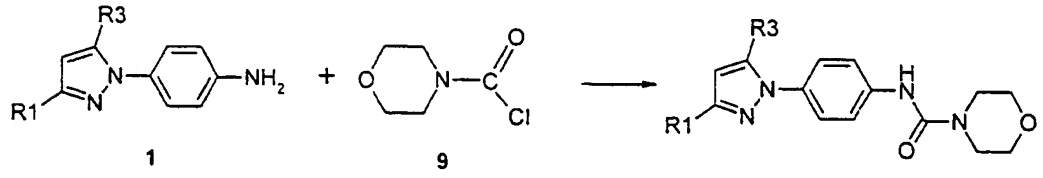
Compounds in which L is -NHC(O)NH- may be prepared by reaction of isocyanate 7 with an amine 8 in a suitable solvent such as methylene chloride or toluene (Method E). An amine such as triethylamine may be added. Alternatively, 1 could be reacted with an amine carbonyl chloride such as N-morpholine carbonyl chloride 9 in a suitable solvent such as methylene chloride (Method F).

Method E



7 8

Method F



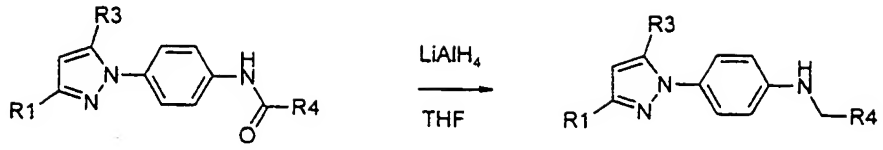
1 9

Methods by which compounds in which L is -NHCH(R_5)- or –NHCH$_2$ may be prepared as illustrated below. For example, these compounds may be prepared by reduction of the corresponding amide (L is -NHC(O)-) with a suitable reducing agent such as lithium aluminum hydride, in a suitable solvent such as THF or diethyl ether (Method G). Alternatively, amine 1 could react with an alkylating agent 10 (Method H) where X is a suitable leaving group such as a halogen. In another alternate procedure, amine 1 could react with an aldehyde 11. and the intermediate imine 12 reacted with a reducing agent such as

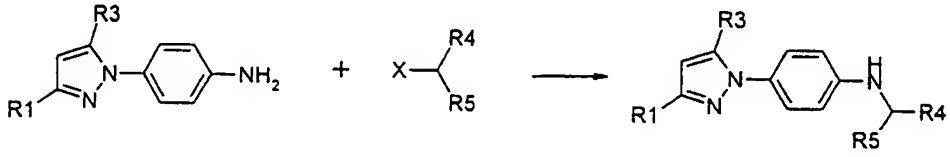
sodium cyanoborohydride or sodium triacetoxyborohydride (Method I). Alternatively, **12** could be reacted with a nucleophile such as an alkyl or aryl lithium reagent (Method J).

Pyrazole intermediates used in the preparations of the compounds of the invention may be prepared by methods known in the chemical literature. Two general methods that may be used are illustrated below. For example, a disubstituted 1,3-dione **13** may be heated with 4-nitrophenylhydrazine in a suitable solvent such as ethanol to provide a 3,5-disubstituted 1-(4-nitrophenyl)pyrazole. If R_1 and R_3 are not equivalent, a mixture of two

M thod G

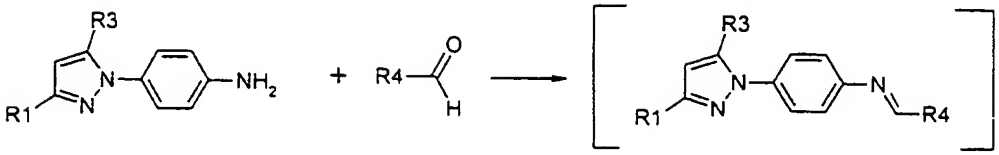


Method H

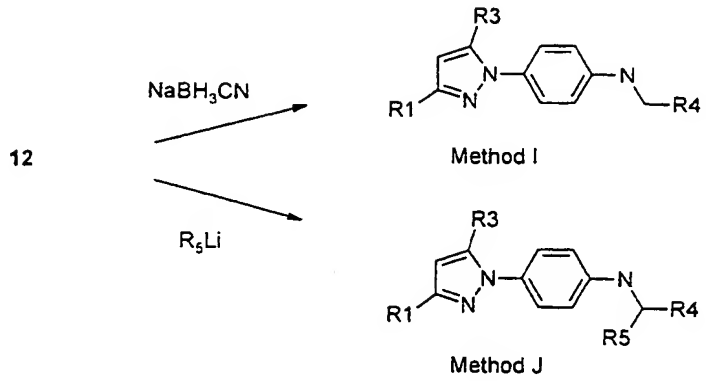


1 10

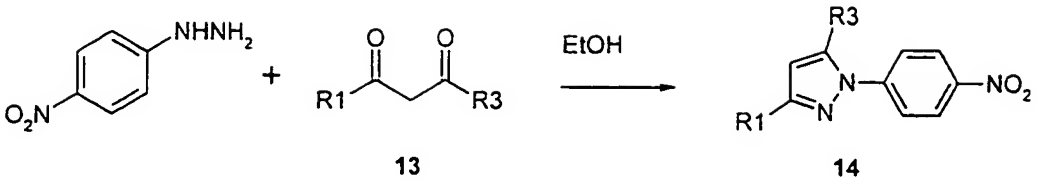
Methods I and J



1 11 12

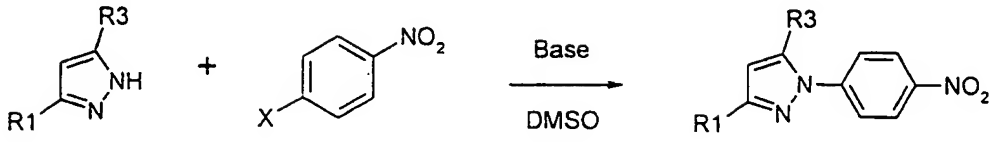


Method K

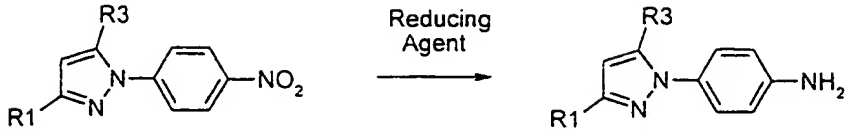


13 14

Method L



14



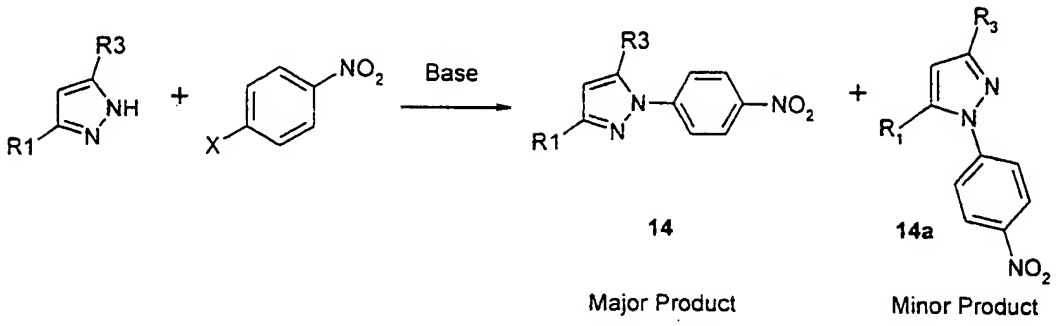
14 1

products may be obtained (Method K). Alternately, a 3,5-disubstituted pyrazole may be reacted with nitrobenzene substituted in the 4-position with a leaving group such as a halogen in the presence of a base (Method L). The nitrophenylpyrazoles produced by either method could then be reduced to aminophenyl pyrazoles by using a reducing agent such as $SnCl_2$ or hydrogen or a hydrogen source such as ammonium formate in the presence of a catalyst such as palladium.

Certain R_1 and R_3 can greatly enhance the regioselectivity of the reaction to produce **14** by Method L. If R_1 is aryl, and preferably an electron deficient aryl, such as pyridine, or a phenyl with an electron withdrawing group such as –CN or NO_2, and R_3 is alkyl, preferably ethyl or methyl, high regioselectivity to give **14** as the major product compared to regioisomer **14a** can be obtained (Scheme I) by reacting the substituted pyrazole with a nitrobenzene substituted in the 4-position with a leaving group, preferably fluorine in a

suitable solvent, preferably DMSO, with a suitable base, preferably *t*-BuOK at about 75 °C for about one hour.

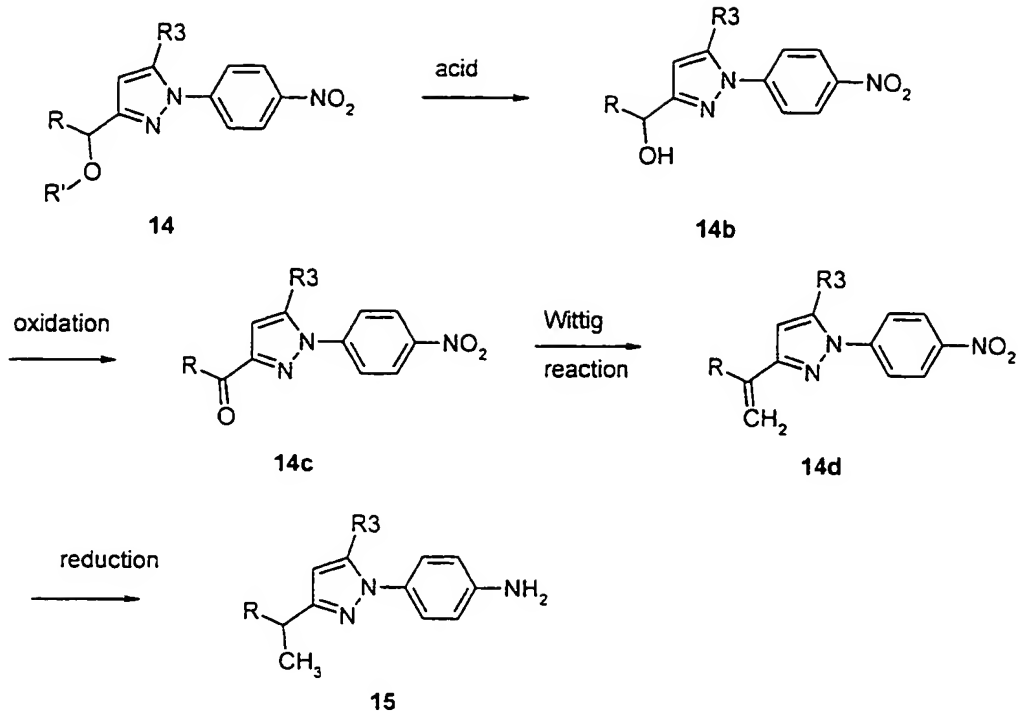
Scheme I



One may obtain **14** where R_1 is alkyl in a regioselective manner using Method L, by employing a substituted pyrazole where R_1 contains a chelating group, preferably oxygen, and then converting R_1 in the resulting product **14** to an alkyl group. For example, as illustrated in Scheme I, reacting a substituted pyrazole where R_1 is an alkylcarbonyl, preferably -$C(O)CH_3$, or an ether such as CH(R)OR', where R is preferably hydrogen or methyl, and R' is a suitable protecting group, preferably tetrahydropyranyl (THP) with a nitrobenzene substituted in the 4-position with a leaving group, preferably fluorine, in a suitable solvent, such as THF or DMSO, preferably THF in the presence of a suitable base such as *t*-BuOK, n-BuLi, sodium hydride, or ethyl magnesium bromide, preferably *t*-BuOK, one obtains regioisomer **14** as the major product.

R_1 may be converted to an alkyl group as illustrated in Scheme II

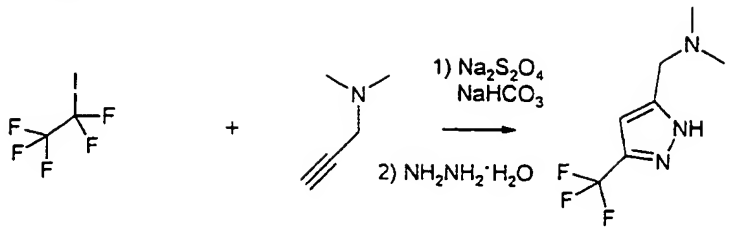
Scheme II



As shown for **14** where R_1 is an ether and R' = THP, reaction with an acid, such as *p*-toluenesulfonic acid in a suitable solvent such as aqueous methanol provides alcohol **14b**. Treatment with a suitable oxidizing agent such as pyridinium chlorochromate provides ketone **14c**. Wittig reaction with a phosphorous ylide derived from methyltriphenylphosphonium bromide provides olefin **14d**. Reaction under reducing conditions, such as hydrogenation in the presence of a palladium catalyst provides **15**. Starting with **14** where R_1 is an alkylcarbonyl, one would proceed beginning with **14c**.

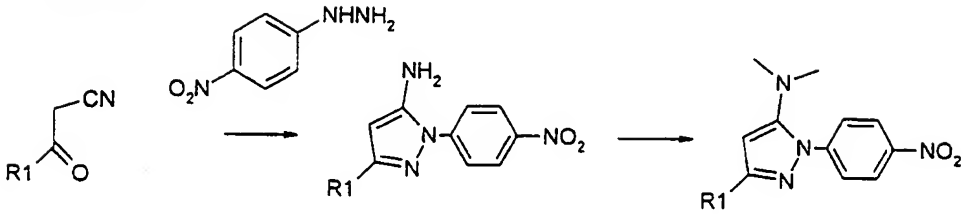
Other methods may also be used for synthesis of pyrazole intermediates. Some of these approaches are illustrated below. 5-Dimethylaminomethylpyrazole **16** may be prepared by a general method (Method M) described in the chemical literature (Tang and

Method M



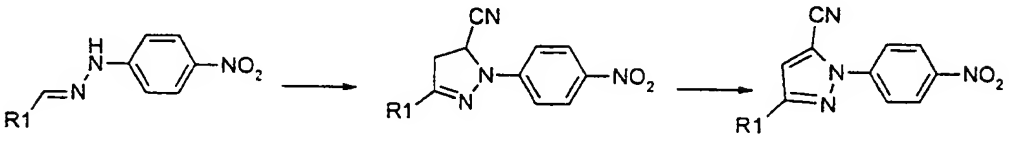
16

Method N



17 18 19

Method O

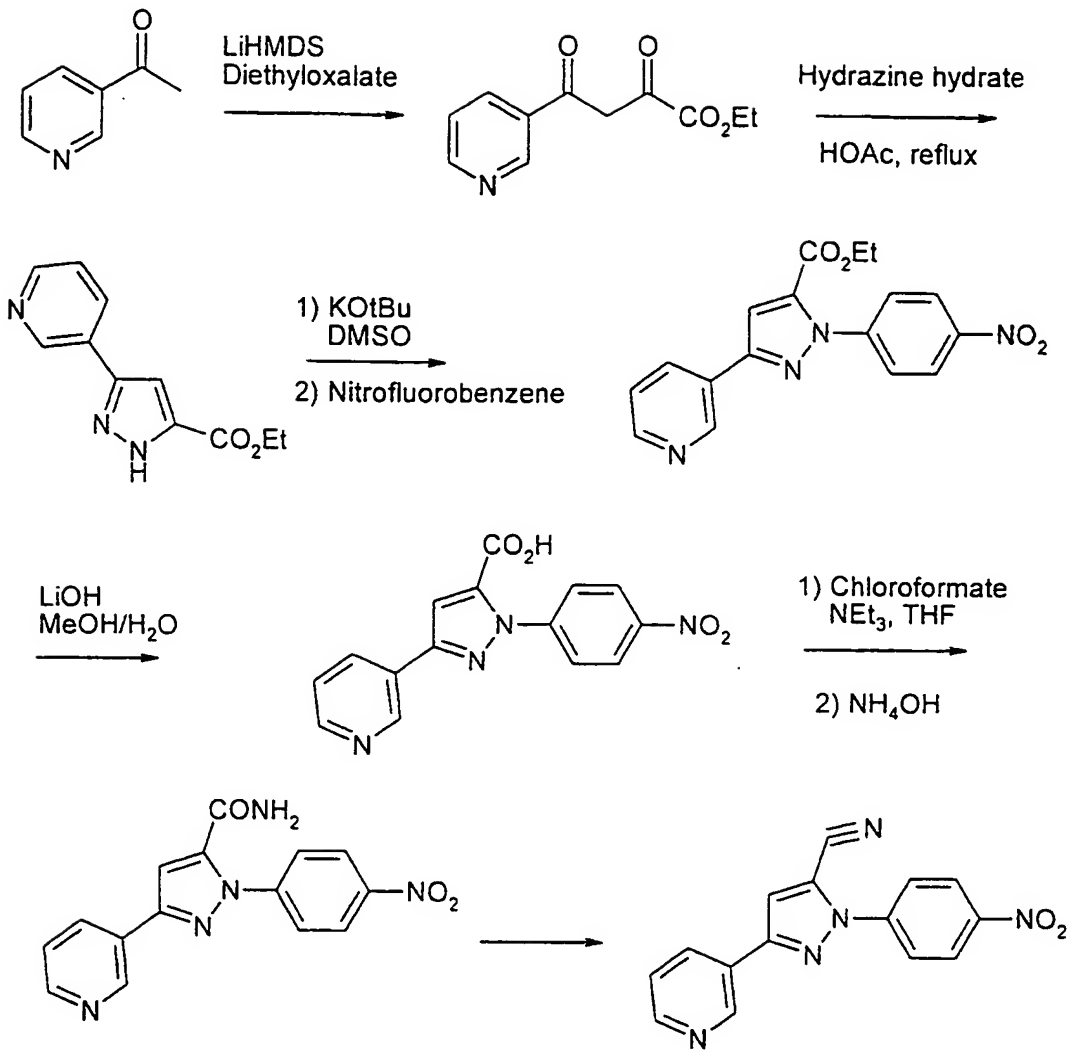


20 21 22

Hu, 1994, J. Chem. Soc. Chem. Commun., 631). The 1-(4-aminophenyl)pyrazole analog of **16** may then be prepared as described in Method L. Using nitrile **17** and 4-nitrophenylhydrazine, the 5-amino and 5-disubstituted aminopyrazoles **18** and **19** can be prepared (Method N). Reaction of hydrazone **20**, with acrylonitrile and iodobenzene diacetate, followed by oxidation of pyrazoline **21** provides 5-cyanopyrazoles **22** (Method O). The nitrophenylpyrazoles described in Methods N and O can then be reduced to the aminophenylpyrazoles as described in Method L.

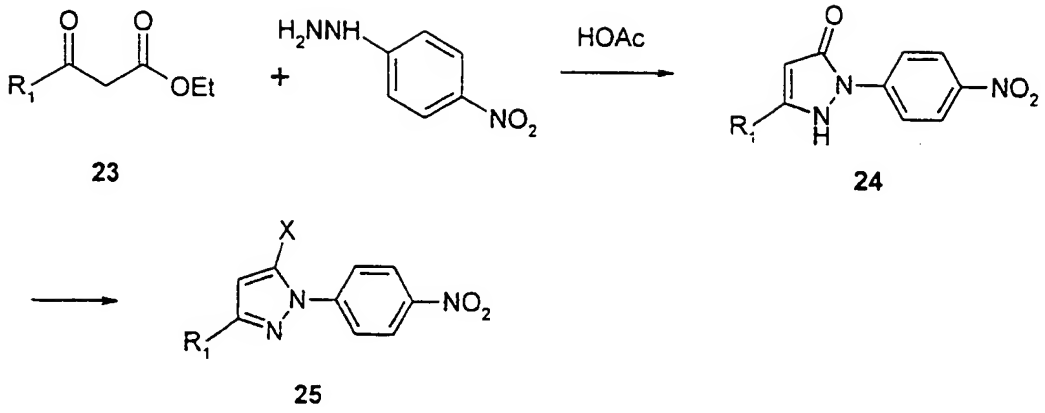
5-Cyanopyrazoles may also be obtained by method P below.

Method P



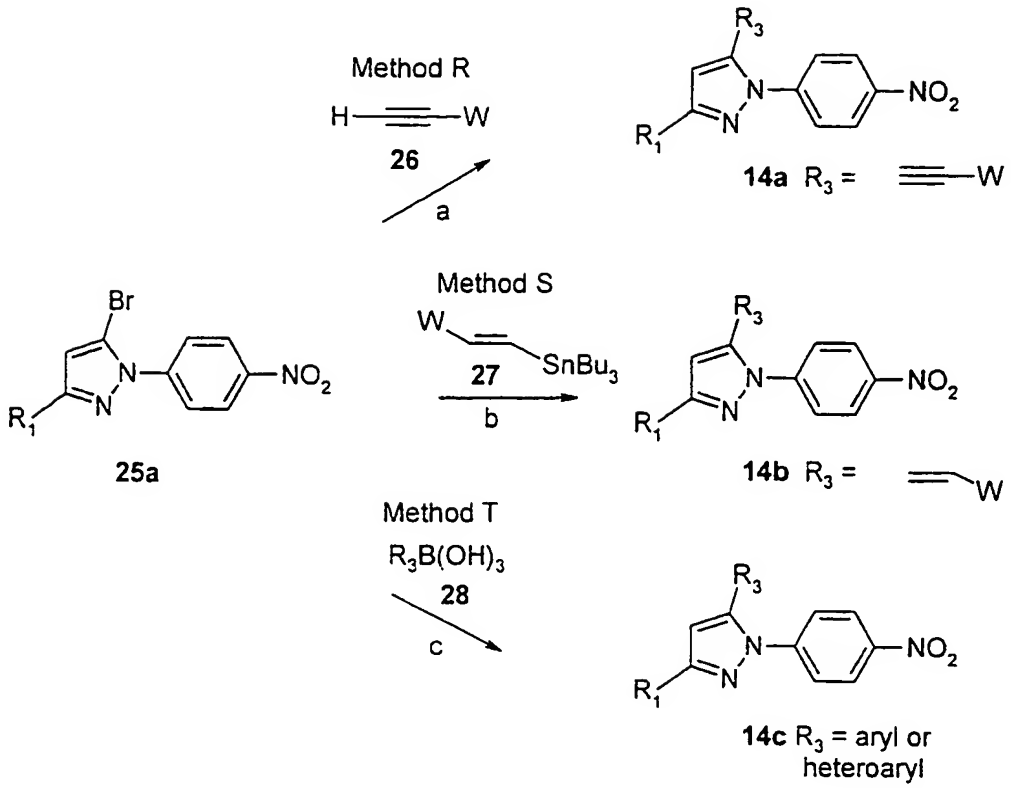
Another procedure where one may regioselectively prepare substituted arylpyrazoles is illustrated by Method Q.

Method Q



Reaction of ketoester **23** with 4-nitrophenylhydrazine in a suitable solvent, preferably acetic acid at about reflux temperature provides **24**. Treatment with a halogenating agent such as phosphorous tribromide or phosphorous oxychloride provides **25** where X = Br or Cl respectively. If desired, **25** (preferably X = Br) may be elaborated further, for example by transition metal catalyzed cross coupling reactions.

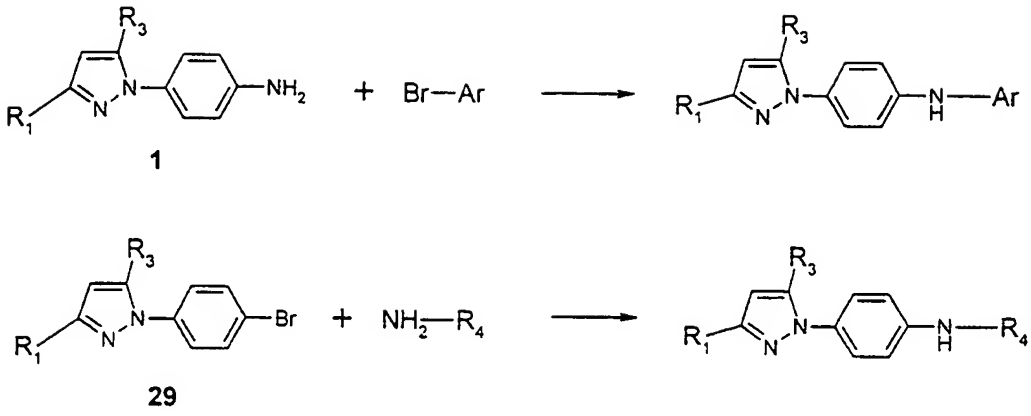
For example, as illustrated in Method R, **25a** may be cross coupled with a terminal acetylene **26**, where W may be, for example, hydrogen, or an alkyl group or any other group not adversely affecting the reaction, using conditions described by T. Sakamoto et al., (Synthesis, 1983, 312) to provide an alkyne at R_3 (**14a**). Alternatively, reaction with vinylstannanes **27**, W defined as above, under conditions described by J.W. Stille (Angew. Chem. Int. Ed. Engl., 1986, 25, 508), provides an alkene at R_3 (Method S). Reaction with substituted or unsubstituted aryl- or heteroarylboronic acids under conditions described by N. Miyaura et al. (Chem. Rev. 1995, 95, 2457) provides **14c** with aryl or heteroaryl groups at R_3 (Method T). Alkynes **14a** and alkenes **14b** may be converted to the corresponding alkyl groups by reduction with a suitable reducing agent such as hydrogen in the presence of a suitable catalyst such as platinum or palladium to provide **1** (see Method L), with an alkyl group at R_3. Alternatively, reaction with a reducing agent that leaves alkenes and alkynes intact, such as $SnCl_2$ provides **1** with alkenes or alkynes at R_3.



a- $Pd(PPh_3)_4$, $CuBrSMe_2$, Et_3N b. $Pd(PPh_3)_4$, THF c. $Pd(PPh_3)_4$, 2M Na_2CO_3, THF

Method U describes an alternate procedure for preparing compounds of Formula I where L is –NH-. Intermediate 1 may be heated at about 70 °C with an aryl bromide in the presence of a palladium catalyst, preferably $Pd_2(dba)_3$, 2,2'-bis(diphenylphosphino)-1,1'-binapthyl (BINAP), and a base, preferably NaO*t*-Bu, in a solvent such as toluene, as described by S. Buchwald et al.(J. Amer. Chem. Soc., 1993, 119, 8451). Alternately, one could employ the same conditions with the bromophenylpyrazole **29** and an amine, R_4NH_2.

Method U



As can be appreciated by chemists possessing ordinary skill in the art, the synthetic schemes described above are for illustrative purposes only and may be modified using conventional synthetic methodology to produce any of the analogs of Formula I. Depending on precisely how the synthetic schemes are modified, the specific reaction conditions might also require modification. Such modifications may involve the use of higher or lower temperature or pressure, conditions other than those reported herein, or the addition of further synthetic steps such as functional group transformations. However, since progress of the reactions is easily monitored by techniques such as high performance liquid chromatography, gas chromatography, mass spectroscopy, thin layer chromatography, nuclear magnetic resonance spectroscopy and the like, such modifications are well within the skill of the art. Likewise, it should be appreciated that initial products from these Methods could be further modified to make additional compounds of this invention. Intermediates used in the Methods described above may be commercially available or could be prepared from commercially available materials by methods described in the chemical literature and known to people skilled in the art.

The 1-phenylpyrazole analogs of Formula I inhibit production of IL-2. Without wishing to be bound by theory, the compounds of this invention inhibit IL-2 production by T cells. This inhibition of IL-2 production is therapeutically useful for selectively suppressing immune function. The result of such selectively suppressed immunity includes reduced cell proliferation of peripheral blood lymphocytes and cellular immune response. Thus, the inhibition of IL-2 production is an attractive means for preventing and treating a variety of immune disorders, including inflammatory diseases, autoimmune diseases, organ and bone marrow transplant rejection and other disorders associated with IL-2 mediated immune response. In particular, the compounds of Formula I may be used to prevent or treat acute or chronic inflammation, allergies, contact dermatitis, psoriasis, rheumatoid arthritis, multiple sclerosis, type 1 diabetes, inflammatory bowel disease, Guillain-Barre syndrome, Crohn's disease, ulcerative colitis, graft versus host disease (and other forms of organ or bone marrow transplant rejection) and lupus erythematosus. Other disorders associated with IL-2 mediated immune response will be evident to those of ordinary skill in the art and can also be treated with the compounds and compositions of this invention.

The compounds of this invention may be administered in any conventional dosage form in any conventional manner. Such methods of treatment, including their dosage levels and other requirements, may be selected by those of ordinary skill in the art from available methods and techniques. For example, a compound of this invention may be combined with a pharmaceutically acceptable carrier or adjuvant for administration to a patient in need of such treatment in a pharmaceutically acceptable manner and in an amount effective to treat (including lessening the severity of symptoms) the immune disorder.

The compounds of this invention may be administered alone or in combination with conventional therapeutics, such as conventional immunosuppressants. Advantageously, such combination therapies utilize lower dosages of the conventional therapeutics, thus avoiding possible toxicity and adverse side effects incurred when those agents are used as monotherapies. The compounds of this invention may be physically combined with the conventional therapeutics into a single pharmaceutical composition. Advantageously, the compounds may then be administered together in a single dosage form. Alternatively, the

compounds may be administered separately (either serially or in parallel). Separate dosing allows for greater flexibility in the dosing regime.

According to this invention, the compounds of Formula I and the pharmaceutical compositions containing those compounds may be administered to a patient in any conventional manner and in any pharmaceutically acceptable dosage from, including, but not limited to, intravenously, intramuscularly, subcutaneously, intrasynovially, by infusion, sublingually, transdermally, orally, topically or by inhalation. The preferred modes of administration are oral and intravenous.

Dosage forms of the compounds of this invention include pharmaceutically acceptable carriers and adjuvants known to those of ordinary skill in the art. These carriers and adjuvants include, for example, ion exchangers, alumina, aluminum stearate, lecithin, serum proteins, buffer substances, water, salts or electrolytes and cellulose-based substances. Preferred dosage forms include, tablet, capsule, caplet, liquid, solution, suspension, emulsion, lozenges, syrup, reconstitutable powder, granule, suppository and transdermal patch. Methods for preparing such dosage forms are known (see, for example, H.C. Ansel and N.G. Popovish, Pharmaceutical Dosage Forms and Drug Delivery Systems, 5th ed., Lea and Febiger (1990)). Dosage levels and requirements are well-recognized in the art and may be selected by those of ordinary skill in the art from available methods and techniques suitable for a particular patient. Typically, dosage levels range from about 10-1000 mg/dose for a 70 kg patient. Although one dose per day may be sufficient, up to 5 doses per day may be given. For oral doses, up to 5000 mg/day may be required. As the skilled artisan will appreciate, lower or higher doses may be required depending on particular factors. For instance, specific dosage and treatment regimens will depend on factors such as the patient's general health profile, the severity and course of the patient's disorder or disposition thereto and the judgment of the treating physician.

Synthetic Examples

In order that this invention be more fully understood, the following examples are set forth. These examples are for the purpose of illustrating preferred embodiments of this invention, and are not to be construed as limiting the scope of the invention in any way.

Example 1: Synthesis of N-{4-[3,5-bis(trifluoromethyl)pyrazol-1-yl]phenyl}cyclohexanecarboxamide (Method A).

A mixture of cyclohexanecarboxylic acid (0.10 g, 0.8 mmol) and EDC (0.077 g, 0.4 mmol) in CH_2Cl_2 (1.5 mL) was stirred for 15 minutes. 1-(4'-Aminophenyl)-3,5-bis(trifluoromethyl)pyrazole (0.059 g, 0.2 mmol) was added followed by dimethylaminopyridine (0.01 g, 0.1 mmol). After 3 hours the mixture was diluted with CH_2Cl_2 (50 mL), washed with 10% $NaHCO_3$ (2x50 mL), brine (3x25mL), and dried over anhydrous Na_2SO_4. Evaporation of the solvent gave the above-named compound as a solid that crystallized from benzene (0.075 g, 92%): mp 178-180 °C; ^1H NMR ($CDCl_3$) δ 1.35 (3H, m), 1.66 (2H, m), 1.75 (1H, m), 1.85 (2H, m), 2.0(2H, m), 2.3 (1H, m), 7.08 (1H, s), 7.45 (1H, d, J = 8.5 Hz), 7.75 (2H, d, J = 8.5 Hz).

Example 2: Synthesis of N-{4-[3,5-bis(trifluoromethyl)pyrazol-1-yl]phenyl}-2-methylbenzamide (Method B).

A mixture of 1-(4'-aminophenyl)-3,5-bis(trifluoromethyl)pyrazole (0.10 g, 0.34 mmol), o-toluoyl chloride (0.062 mL, 0.43 mmol), and triethylamine (0.06 mL, 0.43 mmol) in methylene chloride (7 mL) was stirred under argon for three days. The reaction mixture was diluted with methylene chloride, washed with 1N hydrochloric acid (2x50 mL), brine (2x40 mL), dried (magnesium sulfate) and concentrated to give an off-white solid. Recrystallization from methylene chloride / hexanes gave the above-named compound (0.065 g). m.p. 175 °C. NMR ($CDCl_3$, 400MHz): δ 7.83(d, 2H), 7.64 (br s, 1H), 7.53(m, 3H), 7.43(m, 1H), 7.31(m, 2H), 7.10(s, 1H), 2.56(s, 3H).

Example 3: Synthesis of N-[4-(3,5-Di-*i*-propylpyrazol-1-yl)phenyl]pyridine-3-carboxamide (Method C).

A solution of *p*-(3'-pyridinylcarboxamido)phenylhydrazine hydrochloride (1.5 g, 5 mmol) and 2,6-dimethyl-3,5-heptanedione (0.466 g, 3 mmol) in glacial acetic acid (16 mL) was refluxed for 6 hours. After cooling, the reaction mixture was diluted with water (100 mL) and extracted with EtOAc (2 x 30 mL), washed with aqueous bicarbonate, and water , and dried ($MgSO_4$). The residue obtained was purified by chromatography over silica gel (MeOH/ CH_2Cl_2) to give the above-named compound as a white solid (0.240 g, 23%) m.p. 190-2 ^{0}C. NMR 9.3 (br, 1H); 8.9 (s, 1H); 8.7 (br, 1H); 8.4 (m, 1H); 7.7 (d, 2H); 7.4 (br, 1H); 7.3 (d, 2H); 6.0 (s, 1H); 2.9 (m, 2H); 1.2 (d, 6H); 1.1(d, 6H)..

Example 4: Synthesis of 1-{4-[N-(4-cyanopyridin-2-yl)amino]phenyl}-3,5-bis(trifluoromethyl)pyrazole (Method D)

A mixture of 1-(4'-aminophenyl)-3,5-bis(trifluoromethyl)pyrazole (0.36 g) and 2-chloro-4-cyanopyridine (0.14 g) in dioxane (1 mL) was heated at 125 °C in a sealed tube for 5 days. The mixture was diluted with ethyl acetate and washed with water. The organic phase was dried, filtered and evaporated. Chromatography of the residue over silica gel (methylene chloride to 2% ethanol /methylene chloride gradient gave the above-named compound (0.22 g) mp 152-153 °C NMR ($CDCl_3$) 8.45 (1H, m), 7.86 (3H, m), 7.48 (2H, d), 7.20 (1H, br s), 7.07 (1H, s), 6.91 (1H, m).

Example 5: Synthesis of benzo[d]isoxazol-3-yl-{4-[3,5-bis(trifluoromethyl)pyrazol-1-yl]phenyl}amine (Method D)

To a stirred solution of 1-(4'-aminophenyl)-3,5-bis(trifluoromethyl)pyrazole (0.20 g, 0.68 mmol) and 3-chlorobenzisoxazole (0.10 g, 0.65 mmol) in tetrahydrofuran (2.5 mL) under argon was added sodium bis-trimethylsilyl amide (1.0 M in tetrahydrofuran, 0.68 mL, 0.68 mmol). After seven days, the mixture was diluted with water, and extracted with ethyl acetate. The organic layer was washed with brine, dried (magnesium sulfate) and concentrated. The residue was purified by flash chromatography (elution with ethyl acetate /

hexanes) to give the above-named compound (0.050 g). m.p. 209-210 °C. NMR ($CDCl_3$, 400MHz): δ 7.77 (d, 1H), 7.64 (m, 3H), 7.53 (d, 2H), 7.37 (m, 1H), 7.09 (s, 1H), 6.68 (s, 1H).

Example 6: Synthesis of N-{4-[(3,5-bis(trifluoromethyl)pyrazol-1-yl]phenyl}-N'-cyclohexylurea (Method E)

To morpholinomethyl polystyrene (Novabiochem. substitution = 3.55 mmol/g, 1.02 g, 3.62 mmol) in methylene chloride (18.5 mL) under argon was added 1-(4'-aminophenyl)-3,5-bis(trifluoromethyl)pyrazole (0.555 g, 1.88 mmol). The mixture was cooled to 0 °C and phosgene (1.93M in toluene, Fluka, 1.95 mL,3.76 mmol) was added. After thirty minutes the reaction mixture was filtered, washed with methylene chloride (2x30 mL) and concentrated to give 1-(4'-isocyanatophenyl)-3,5-bis(trifluoromethyl)pyrazole.

The solution of 1-(4'-isocyanatophenyl)-3,5-bis(trifluoromethyl)pyrazole (0.10 g. 0.31 mmol) in methylene chloride (2 mL) was added to cyclohexylamine (0.036 mL, 0.32 mmol) in a stoppered vial. The mixture was stirred at room temperature for two and a half days. The solid product was collected by filtration and washed with methylene chloride to give the title compound (0.061 g) m.p. 185-188 °C. NMR (DMSO, 270MHz): δ 8.84 (s, 1H), 7.79 (s, 1H), 7.58 (d, 2H), 7.44 (d, 2H), 6.34 (d, 1H), 3.49 (m, 1H), 1.71(m, 4H), 1.24 (m, 6H).

Example 7: Synthesis of N-{4-[(3,5-bis(trifluoromethyl)pyrazol-1-yl]phenyl}-N'-[(*R*)-tetrahydro-furan-3-yl]urea (Method E)

Triethylamine (0.05 mL, 0.36 mmol) was added to *R*-(+)-3-aminotetrahydrofuran toluene-4-sulfonate (Fluka, 0.082 g, 0.32 mmol) and 6-8 beads of 4Å molecular sieves in an oven-dried sealed tube. 1-(4'-Isocyanatophenyl)-3,5-di(trifluoromethyl)pyrazole (0.10 g, 0.32 mmol) in toluene (3 mL) was added, and the mixture was capped and stirred at room temperature for two and a half days. The solid product was collected by filtration, and washed with toluene. Purification by preparative TLC (elution with 1:1 ethyl acetate / hexanes) followed by recrystallization from ethyl acetate / hexanes gave the above-named compound as a white solid (0.045 g). m.p. 198-200 °C. NMR ($CDCl_3$, 270MHz): δ 8.74 (s, 1H), 7.79 (s, 1H), 7.58

(d, 2H), 7.46 (d, 2H), 6.60 (d, 1H), 4.23 (m, 1H), 3.76 (m, 3H), 3.57 (m, 1H), 2.15 (m, 1H), 1.75 (m, 1H).

Example 8: Synthesis of morpholine-4-carboxylic acid {4-[3.5-bis(trifluoromethyl)pyrazol-1-yl]phenyl}amide (Method F)

To a solution of 1-(4'-aminophenyl)-3,5-bis(trifluoromethyl)pyrazole (0.300 g, 1.02 mmol) in of methylene chloride (5 mL) was added diisopropylethyl amine (0.18 mL, 1.0 mmol) followed by 4-morpholine carbonylchloride (0.11 mL, 1.0 mmol). The mixture was stirred at rt for 6 days, and diluted with ethyl acetate. It was then washed twice with water, dried over sodium sulfate and evaporated. Chromatography of the residue over silica gel (50% EtOAc / hexanes) gave the above-named compound (0.080 g, 19.6%) as a white solid: mp 185-186 ^{0}C. NMR ($CDCl_3$) δ 7.56 (2H, d). 7.44 (2H, d), 7.07 (1H, s), 6.51 (1H, s), 3.79 (4H, m), 3.54 (4H, m).

Example 9: Synthesis of {4-[3,5-bis(trifluoromethyl)pyrazol-1-yl]phenyl}-3,5-dimethylisoxazol-4-ylmethyl)amine (Method G)

A solution of N-[4-(3,5-bis(trifluoromethyl)pyrazol-1-yl)phenyl]-3,5-dimethylisoxazole-4-carboxamide (0.418 g, 1 mmol) in dry THF (15 mL) was refluxed at 80 ^{0}C with lithium aluminum hydride (1.5 mL of 1 M solution in THF). After 45 minutes the reaction mixture was cooled to room temperature. water (0.3 mL) was added, the mixture was stirred for 5 minutes, the precipitate was removed, and the solvent was evaporated. The residue was taken up in brine (50 mL), and extracted with CH_2Cl_2 (3x25 mL). The combined CH_2Cl_2 extract was washed with brine (3x25 mL), dried over anhydrous Na_2SO_4 and the solvent was evaporated. The residue was purified by flash column chromatography over silica gel (2% acetone in CH_2Cl_2) to give the above-named compound (0.200 g, 50%): mp 94-96 ^{0}C. NMR (DMSO-d6) δ 2.2 (3H, s), 2.38 (3H, s), 4.05 (2H, d, J = 5 Hz), 6.43 (1H, t, J = 5 Hz), 6.7 (2H, d, J = 8 Hz), 7.29 (2H, d, J = 8 Hz) 7.7 (1H, s).

Example 10: Synthesis of {4-[3,5-bis(trifluoromethyl)pyrazol-1-yl]phenyl}ethylamine (Method H)

A mixture of 1-(4'-aminophenyl)-3,5-bis(trifluoromethyl)pyrazole (0.15 g, 0.58 mmol), ethyl iodide (0.10 mL, 1.26 mmol), and Hunig's base (0.20 mL, 1.14 mmol) in N,N-dimethylformamide (10 mL) was heated to 50 °C under argon with stirring. After 24 hours the mixture was diluted with water, and extracted with ethyl acetate. The organic phase was washed with water (4 x 25 mL), brine, dried (magnesium sulfate) and concentrated. The residue was purified by flash chromatography (ethyl acetate / hexanes) followed by recrystallization from ethanol / water to give the above-named compound (0.045 g) as yellow crystals. mp 54 °C. NMR ($CDCl_3$, 400MHz): δ 7.26 (d, 2H), 7.02 (s, 1H), 6.64 (d, 2H), 3.93 (br s, 1H), 3.22 (q, 2H), 1.31 (t, 3H).

Example 11: Synthesis of N-{4-[3,5-bis(trifluoromethyl)pyrazol-1-yl]phenyl}pyridin-4-ylmethylamine (Method I)

A mixture of 1-(4'-aminophenyl)-3,5-bis(trifluoromethyl)pyrazole (0.059 g, 0.2 mmol) and pyridine-4-carboxaldehyde (20 μL, 0.2mmol) in methanol (0.8 mL) and acetic acid (0.2 mL) was stirred at room temperature for 15 minutes Sodium cyanoborohydride (0.032 g, 0.5 mmol) was added, and the reaction mixture stirred overnight. The reaction mixture was diluted with CH_2Cl_2 (50 mL), washed with brine (2x20 mL), dried over anhydrous Na_2SO_4 and evaporated. The residue was purified by flash column chromatography over silica gel (2% acetone in CH_2Cl_2) to give the above-named compound (0.060 g, 78%): mp 92-94 °C. NMR (DMSO-d6) δ 4.40 (2H, d) , 6.65 (2H, d), 6.97 (1H, t), 7.23 (2H, d), 7.35 (2H, d), 6.65 (2H, d), 7.7 (1H, s), 8.51 (2H, d).

Example 12: Synthesis of {4-[3,5-bis(trifluoromethyl)pyrazol-1-yl]phenyl}-(1-phenylethyl)amine (Method J)

A mixture of 1-(4'-aminophenyl)-3,5-bis(trifluoromethyl)pyrazole (1.5 g), benzaldehyde (0.53 g) and tosic acid (0.03 g) in toluene (20 mL) was heated under a Dean Stark apparatus at 140 °C for 3 hours. The mixture was filtered and evaporated to dryness to give N-

(benzylidene)-1-(4'-aminophenyl)-3,5-bis(trifluoromethyl)pyrazole as a solid (1.4 g) which was used without further purification.

To the stirred imine (0.19 g) in THF under argon at rt was added a solution of methyl lithium (1.6 M in ether, 0.8 mL). After 5 minutes, water (0.2 mL) was added. The mixture was extracted with hexane, and the organic phase was dried, filtered and evaporated. Chromatography of the residue over silica gel (methylene chloride / hexane) gave the above-named compound as an oil that solidified on trituration with cold hexane ((0.115 g): mp 58-61 °C. NMR ($CDCl_3$) 7.35-7.21 (m, 5H), 7.15 (2H, d), 6.98 (1H, s), 6.53 (2H, d), 4.52 (1H, q), 4.38 (1H, br s), 1.55 (3H, s).

Example 13: Synthesis of 1-(4'-aminophenyl)-3-*t*-butyl-5-trifluoromethylpyrazole and 1-(4'-aminophenyl)-5-*t*-butyl-3-trifluoromethylpyrazole (Method K)

A mixture of 1,1,1-trifluoro-5,5-dimethylhexane-2,4-dione (5.9 g, 30 mmol) and 4-nitrophenylhydrazine (5.1g, 30 mmol) in ethanol (75 mL) was heated at 80 °C for 6 hours. The solvent was evaporated, and the residue was treated with neat trifluoroacetic acid (150 mL) for 2 hours. The residue, after evaporation of trifluoroacetic acid, was taken up in aqueous $NaHCO_3$ (250 mL), and extracted with CH_2Cl_2 (3x100 mL). The combined extract was washed with water, dried over anhydrous Na_2SO_4 and evaporated to give a 4:1 mixture of 1-(4'-nitrophenyl)-3-t-butyl-5-trifluoromethylpyrazole and 1-(4'-nitrophenyl)-5-t-butyl-3-trifluoromethylpyrazole (10 g).

To a stirred solution of the mixture of nitro compounds (1 g) in methanol (50 mL) and acetic acid (1 mL) was added 10% Pd/C (0.24 g) followed by ammonium formate (0.2 g). The mixture was stirred at room temperature for 30 minutes. The catalyst was removed by filtration, and the solvent was evaporated. The residue was taken up in 10% $NaHCO_3$ and the solid precipite was collected by filtration, washed with water, and dried under vacuum to give a mixture of 1-(4'-aminophenyl)-3-t-butyl-5-trifluoromethylpyrazole and 1-(4'-aminophenyl)-5-*t*-butyl-3-trifluoromethylpyrazole (0.87 g).

Example 14: Synthesis of 1-(4'-nitrophenyl)-3-phenyl-5-ethyl-1H-pyrazole (Method L)

To a solution of 3-phenyl-5-ethylpyrazole (1.0 g, 5.8 mmol) in DMSO (5 mL) was added potassium *t*-butoxide (0.72 g, 6.4 mmol) followed by 4-fluoronitrobenzene (0.65 mL, 6.4 mmol). The mixture was heated at 90 °C for 1 hour, cooled to rt, and quenched with water (50 mL). The precipitate was collected by filtration, redissolved in ethyl acetate (50 mL), treated with active carbon (3 g), and filtered through diatomaceous earth. The mixture was concentrated to 5 mL, and hexane (25 mL) was added. The 1-(4'-nitrophenyl)-3-phenyl-5-ethylpyrazole was collected by filtration (1.70 g, 92%): mp 112-113 °C. NMR 8.39 (2H, d), 7.79 (2H, d), 7.90 (2H, m), 7.45 (2H, m), 7.38 (1H, m), 6.66 (1H, s), 2.86 (2H, q), 1.38 (3H, t).

Example 15: Synthesis of 1-(4'-aminophenyl)-5-dimethylamino-3-trifluoromethylpyrazole (Method M)

To a solution of *N,N*-dimethylpropargyl amine (20 mmol) and perfluoroethyl iodide (20 mmol) in MeCN / H_2O (35 mL, 4:3), cooled to 0 °C, was added slowly a solution of $Na_2S_2O_4$ (20 mmol) and $NaHCO_3$ (20 mmol) in H_2O (10 mL). After 20 minutes, volatile material was removed, and the residue was extracted with Et_2O. The organic phase was washed with brine, dried over $MgSO_4$, and evaporated to give the crude iodoalkene as a yellow oil (2.85 g, 43 %). A mixture of the iodoalkene (8.5 mmol) and NH_2NH_2*H_2O (42.5 mmol) in EtOH (13 mL,) was heated under reflux for 5 hours. The solvent was removed, and the residue was partitioned between $NaHCO_3$ and CH_2Cl_2. The organic phase was washed with brine, dried over $MgSO_4$, and evaporated to give 5-dimethylamino-3-trifluoromethylpyrazole (0.65 g, 40%).

5-Dimethylamino-3-trifluoromethylpyrazole (2.9 mmol) was reacted with 4-nitrofluorobenzene (2.9 mmol), as described in Method L, to give 1-(4'-nitrophenyl)-5-dimethylamino-3-trifluoromethylpyrazole which was purified by chromatography over silica gel (hexanes / EtOAc, 8:2) (0.423 g, 46%). The nitrophenylpyrazole (1.35 mmol) was reduced by phase transfer hydrogenation, described generally in Method L, to give 1-(4'-aminophenyl)-5-dimethylamino-3-trifluoromethylpyrazole as an off-white solid (0.321 g, 84%).

Example 16: Synthesis of 1-(4'-aminophenyl)-3-*t*- butyl-5-dimethylaminopyrazole (Method N)

A mixture of *t*-butylacetoacetonitrile (10 mmol) and *p*-nitrophenylhydrazine (10 mmol) in EtOH (20 mL) was stirred at reflux overnight. The solvent was removed and the residue was partitioned between CH_2Cl_2 and brine. The organic phase was dried over $MgSO_4$, and evaporated. Chromatography over silica gel (hexanes / CH_2Cl_2/ MeOH, 20:79:1) gave 1-(4'-nitrophenyl)-3-t-butyl-5-aminopyrazole (0.950 g, 36%).

A mixture of 1-(4'-nitrophenyl)-3-t-butyl-5-aminopyrazole (1 mmol) and formaldehyde (10 mmol, 37% w/w in H_2O) in MeOH (7.5 mL) was stirred at rt for 30 minutes. Acetic acid (2.5 mL) and $NaCNBH_3$ (2 mmol) were added, and after 1 hour additional $NaCNBH_3$ (2 mmol) was added. After 1 hour, 1N H_2SO_4 was added, the solvent was removed and the residue was neutralized with $NaHCO_3$. The solid product was collected by filtration, washed with water and dried to give 1-(4'-nitrophenyl)-3-t-butyl-5-dimethylaminopyrazole (0.265 g, 92%). Transfer hydrogenation of the nitro compound (0.89 mmol) as described in general in Method L gave 1-(4'-aminophenyl)-3-t-butyl-5-dimethylaminopyrazole (0.228 g, 100%).

Example 17: Synthesis of 1-(4'-aminophenyl)-5-pyridin-2-yl-3-cyanopyrazole (Method O)

To a suspension of the hydrazone (2.43 g) prepared from pyridine-2-carboxaldehyde and 4-nitrophenylhydrazine in acetonitrile (50 mL) and methylene chloride (30 mL) cooled to 0 °C was added dropwise a solution of iodobenzenediacetate (3.35 g) in methylene chloride (30 mL). The mixture was allowed to warm to rt and stirred overnight. Hexane (100 mL) was added and the solid product 1-(4'-nitrophenyl)-5-(2'-pyridinyl)-3-cyanopyrazoline (2.74 g) was collected by filtration.

To a suspension of the pyrazoline (1.52 g) in methylene chloride (60 mL) cooled on ice was added lead tetraacetate (85%, 2.6 g). The mixture was allowed to warm to rt and stirred for 3

days. The mixture was filtered through diatomaceous earth, and evaporated. Chromatography of the residue over silica gel (methylene chloride / ethanol 99:1 –93:7) gave product 1-(4'-nitrophenyl)-5-(2'-pyridinyl)-3-cyanopyrazole (1.01 g).

A mixture of 1-(4'-nitrophenyl)-5-(2'-pyridinyl)-3-cyanopyrazole (0.50 g), 10% Pd/C (0.20 g) and ammonium formate (3.0 g) in ethanol (20 mL) was stirred under argon for 4 hours. The mixture was filtered through diatomaceous earth and the solvent was evaporated. The residue was taken up in chloroform / water, and the organic phase was separated, dried and evaporated to give the crude 1-(4'-aminophenyl)-5-(2'-pyridinyl)-3-cyanopyrazole which was used without further purification.

Example 18: 5-Cyano-3-(3-pyridyl)-1-(4'-aminophenyl)pyrazole (Method P)

A solution of 3-acetylpyridine (11 mL, 100 mmol) and diethyl oxalate (16.5 mL, 120 mmol) in anhydrous THF (200 mL), under an argon atmosphere, was cooled to –78°C. LiHMDS (110 mmol, 1 M in THF) was added and the reaction allowed to slowly warm to room temperature. After 3.5 hrs, volatiles were removed under reduced pressure and the residue was dried under high vacuum overnight. Crude solids were taken up in HOAc (200 mL), treated with hydrazine monohydrate (3.9 mL, 110 mmol) and heated overnight at 90°C. The reaction was allowed to cool to room temperature, volatiles were removed under reduced pressure and residue taken up in aqueous $NaHCO_3$. Solids were filtered, washed with water and dried to give a mixture of isomers containing 5-ethoxycarbonyl-3-(3-pyridyl)pyrazole (17.4 g, 80%).

KO*t*-Bu (9.9 g, 88 mmol), under argon atmosphere, was dissolved in DMSO (180 mL) and stirred for 5 minutes. The above pyrazole (17.4 g, 80 mmol) was added and reaction stirred for 10 min. 4-Nitro-1-fluorobenzene (9.4 mL, 88 mmol) was added and the reaction mixture was stirred and heated overnight at 80 °C. After cooling to room temperature, DMSO was removed under reduced pressure and the residue was taken up in ice. Precipitated solids were filtered, washed with water and dried. Crude pyrazole was taken up in MeOH (320 mL) and water (80 mL) and treated with $LiOH{\cdot}H_2O$ (5 g, 120 mmol). Reaction was complete after 1.5 hrs. Volatiles were removed and the aqueous layer neutralized to pH 5 with 1N H_2SO_4.

Precipitated solids were filtered, washed with water and dried overnight in vacuum oven to yield 12.7 g (41 %) of a mixture containing 5-carboxy-3-(3-pyridyl)-1-(4'-nitrophenyl)pyrazole.

5-Carboxy-3-(3-pyridyl)-1-(4'-nitrophenyl)pyrazole (12.7 g, 41 mmol) was suspended in THF (400 mL) and treated with triethylamine (6.9 mL, 49 mmol). The reaction mixture was cooled to –10 °C, treated with isobutylchloroformate (6.4 mL, 49 mmol) and stirred for 45 minutes. Concentrated ammonium hydroxide (3.6 mL, 53 mmol) was added and the reaction mixture was allowed to slowly warm to room temperature and stirred overnight. Volatiles were removed under reduced pressure and the residue was taken up in water. Solids were filtered, washed with water, and dried in vacuum oven to give a mixture of isomers containing 5-carboxamido-3-(3-pyridyl)-1-(4'-nitrophenyl)pyrazole (9.6 g, 76%).

5-Carboxamido-3-(3-pyridyl)-1-(4'-nitrophenyl)pyrazole (9.6 g, 31 mmol) was suspended in DMF (300 mL), cooled to 0 °C and treated with $POCl_3$ (5.8 mL, 62 mmol). The mixture was heated at 80 °C 1 hr, then cooled to room temperature. The volatiles were removed under reduced pressure, the residue was taken up in aqueous $NaHCO_3$ and resulting solids were filtered, washed with water and dried. 5-Cyano-3-(3-pyridyl)-1-(4'-nitrophenyl)pyrazole (2.8g) was eluted from a silica gel column with CH_2Cl_2/MeOH 95:5. Impure fractions were concentrated and washed with diethyl ether to give an additional 1.5 g, for a total of 4.3 g of product (48%).

5-Cyano-3-(3-pyridyl)-1-(4'-nitrophenyl)pyrazole (4.3 g, 15 mmol) was added to stirred slurry of $SnCl_2 \cdot H_2O$ (20 g, 90 mmol) in HCl/HOAc (35 mL/35 mL). A thick suspension formed and was stirred overnight. The reaction mixture was carefully basified with 50% NaOH to pH 13. The resulting solids were filtered, washed with water and dried to give the title compound (3.9 g, 99%).

Example 18: Synthesis of 1-(4-Nitrophenyl)-3-hydroxymethyl-5-ethylpyrazole (Method L, Scheme I).

To a solution of 3-(tetrahydropyran-2-yloxy)methyl-5-ethylpyrazole (27.0 g, 0.13 mol) in dry THF (250 mL) was added tert-BuOK (14.4g, 0.13 mol) under nitrogen. After 10 min, 4-fluoronitrobenzene (18.1 g, 0.13 mol) was added. The mixture was heated to reflux for 10 hr, the solvent was then removed under vacuum The residue was taken up in ethyl acetate and washed with water, The organic layer was dried over $MgSO_4$ and filtered. The filtrate was treated with active carbon (3.0 g, norit A alkaline) at reflux for 10 min and filtered through a pad of diatomaceous earth. The filtrate was concentrated to give a crude 7:1 mixture of regioisomers, which was dissolved in a 10:1 mixture of methanol and water (175 mL) and p-toluenesulfonic acid (1.2 g, 6.4 mmol) was added. The solution was stirred at room temperature for 12 hours and concentrated. The residue was taken up in ethyl acetate and washed with water. The organic layer was dried over $MgSO_4$, filtered and concentrated to a crude solid. Recrystallization in a 1:1 mixture of hexane and ethyl acetate gave the title compound (15.6 g, 45%). mp: 151-152°C.

Example 19: Synthesis of 1-(4-Nitrophenyl)-3-isopropenyl-5-ethylpyrazole (Method L, Scheme II)

1-(4-Nitrophenyl)-3-(1-hyroxyethyl)-5-ethylpyrazole was prepared by the method described in Example 18, yield: 62%. mp: 127-128°C. To a solution of this alcohol (3.30 g, 12.6 mmol) in CH_2Cl_2 (50 mL) was added diatomaceous earth (1.0 g) and pyridinium chlorochromate (3.26 g, 15.2 mmol) and the mixture was stirred at room temperature for 2 hours and filtered. The filtrate was concentrated. The light yellow solid was washed with 10:1 mixture of hexane and ethyl acetate to give 1-(4-nitrophenyl)-3-acetyl-5-ethylpyrazole (3.00 g, 91%) mp: 93-95°C.

To a solution of methyl triphenylphosphonium bromide (3.47 g, 9.72 mmol) in THF (20 mL) was added 1 M KO*t*-Bu in THF (9.73 mL, 9.73 mmol) followed by the above ketone (2.10 g, 8.10 mmol). The mixture was stirred at room temperature for 4 hrs, quenched with water and extracted with ethyl acetate. The extract was dried over Na_2SO_4 and concentrated. The residue

was slurried with hexane and filtered. The filtrate was concentrated to give the title compound as a white solid (1.46 g, 70%). mp: 61-63°C.

Example 20: Synthesis of 1-(4'-aminophenyl)-5-chloro-3-trifluoromethylpyrazole (Method Q)

A mixture of p-nitrophenylhydrazine (6.372 g) and ethyl trifluoroacetoacetate (6 mL) in acetic acid (40 mL) was heated at reflux for 3 hours. After cooling to room temperature, water (40 mL) was added and the 1-(4'-nitrophenyl)-3-trifluoromethyl-5-pyrazolone (9.45 g) was collected by filtration. A mixture of 1-(4'-nitrophenyl)-3-trifluoromethyl-5-pyrazolone (1.43 g) and phosphorus oxychloride (2.8 g) in a sealed tube was heated at 150 °C for 10 hours. The mixture was cooled, and poured onto ethyl acetate / aqueous sodium bicarbonate. The organic phase was separated, washed with dilute HCl, dried, filtered and evaporated. Chromatography of the residue over silica gel (methylene chloride / hexane) gave 1-(4'-nitrophenyl)-5-chloro-3-trifluoromethylpyrazole (0.31 g).
1-(4'-Aminophenyl)-5-chloro-3-trifluoromethylpyrazole was obtained by stannous chloride reduction of the nitro compound as generally described in Method L.

Example 21: Synthesis of 1-(4'-nitrophenyl)-5-(2-triisopropylsilylethynyl)-3-methylpyrazole (Method R)

To a solution of 1-(4'-nitrophenyl)-5-bromo-3-methylpyrazole (prepared as described for Example 19 except using ethyl acetoacetate instead of ethyl trifluoroacetoacetate and using PBr_3 in acetonitrile and refluxing for 72 hr for the halogenation step) (100 mg, 0.35 mmol) in triethylamine (5 mL) was added $Pd(PPh_3)_4$ (20 mg, 0.017 mmol) and $CuBrSMe_2$ (8 mg, 0.036 mmol), followed by triisopropylsilylacetylene (72 mg, 0.39 mmol). The mixture was heated to 70°C for 1 hour and cooled to room temperature. The solid was filtered off and the filtrate was concentrated. The residue was purified by column chromatography on silica gel (hexane/acetate, 4:1) to give the title compound (127 mg, 95%). mp: 71-73°C.

Example 22: Synthesis of 1-(4'-nitrophenyl)-5-ethenyl-3-methylpyrazole (Method S)

To a solution of 1-(4'-nitrophenyl)-5-bromo-3-methylpyrazole (138 mg, 0.49 mmol) in THF (5 mL) was added $Pd(PPh_3)_4$ (21 mg, 0.018 mmol) followed by vinyl tributyltin (0.16 mL, 0.54 mmol). The mixture was heated at reflux for 6 hr under N_2, and was then quenched with saturated KF and extracted with EtOAc. The extract was dried over $MgSO_4$ and concentrated. The residue was purified by column chromatography on silica gel (hexane/acetate, 10:1) to give the title compound (103 mg, 92%).

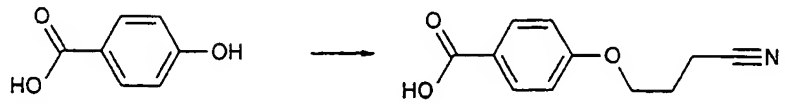
Example 23: Synthesis of 1-(4'-nitrophenyl)-5-(4-methoxyphenyl)-3-methylpyrazole (Method T)

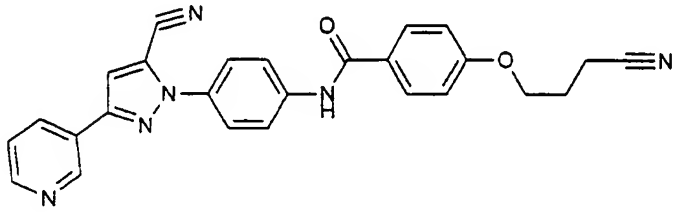
To a solution of 1-(4'-nitrophenyl)-5-bromo-3-methylpyrazole (100 mg, 0.35 mmol) in THF (5 mL) was added $Pd(PPh_3)_4$ (20 mg, 0.017 mmol) and 4-methoxyphenylboronic acid (60 mg, 0.39 mmol), followed by 2 M Na_2CO_3 (0.35 mL, 0.70 mmol). The mixture was heated to reflux for 4 hr, and was then quenched with water and extracted with EtOAc. The extract was dried over $MgSO_4$ and concentrated. The residue was purified by column chromatography on silica gel (hexane/acetate, 15:1) to give the title compound (102 mg, 94%). mp: 155-158°C.

Example 24: Synthesis of {4-[5-Ethyl-3-(3-pyridyl)pyrazol-1-yl]phenyl} 2-(*R*)-indanylamine Method U

A solution of 1-(4-bromophenyl)-5-ethyl-3-(3-pyridyl)pyrazole (obtained by nucleophilic displacement on 1-fluoro-4-bromobenzene by the pyrazole) (100 mg, 0.3 mmol, (R)-1-aminoindane (46 µL, 0.36 mmol), $Pd_2(dba)_3$ (0.50 mg, 0.0006 mmol), (+/-)-BINAP (7.5 mg, 0.012mmol) and sodium t-butoxide (41 mg, 0.42mmol) in toluene (3 mL) was heated in a sealed tube under argon atmosphere at 70°C for 20 h. The reaction mixture was diluted with water, extracted with ethyl acetate, the organic extract with washed with brine and dried ($MgSO_4$). The oil obtained was flash chromatographed (40% ethyl acetate/ hexane) to obtain the title compound as a yellow oil (0.096 g).

Example 25: Synthesis of 4-(3-cyanopropoxy)-N-[4-(5-cyano-3-pyridin-3-yl-pyrazol-1-yl)phenyl]benzamide

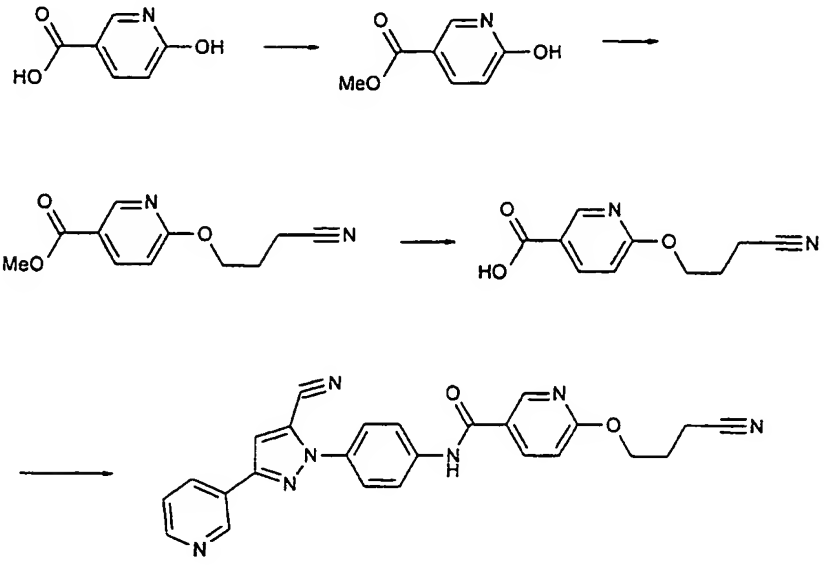




To a stirred solution of 4-hydroxybenzoic acid (40 mmol) in absolute EtOH (350 mL) was added solid NaOEt (84 mmol). After 15 minutes, 4-bromobutyronitrile (40 mmol) was added and the mixture was heated overnight at 90°C on an oil bath. The mixture was cooled to room temperature, volatiles were removed, the residue was taken up in ice and adjusted to pH 6 with 1N sulfuric acid. Solids were collected by vacuum filtration, washed with water and dried to give 4-(cyanopropyloxy)benzoic acid (4.8 g, 58%).

The 4-(cyanopropyloxy)benzoic acid (0.75 mmol) was coupled with 3-(3-pyridyl)-5-cyano-1-(4'-aminophenyl)-pyrazole (0.5 mmol) under standard EDC mediated conditions (Method A). The crude product was recrystallized from hot benzene /methanol, m.p. 193-194°C ^{1}H NMR($CDCl_3$): δ 2.04-2.11(m, 2 H), 2.68-2.71(7, J=7.1 Hz, 2 H), 4.14-4.17(t,J=6 Hz, 2 H), 7.11-7.13(d, J=8.6 Hz, 2 H), 7.53-7.56(m, 1 H), 7.79-7.82(d, J=8.7 Hz, 2 H), 8.00-8.05(m, 4 H), 8.1(s, 1 H), 8.30-8.32(d, J=8 Hz, 1 H), 8.63-8.64(d, J=4.6 Hz, 1 H), 9.15(s, 1 H), 10.4(s, 1 H).

Example 26: Synthesis of 6-[(3-cyanopropoxy)]-N-[4-(5-cyano-3-pyridin-3-yl-pyrazol-1-yl)phenyl]nicotinamide



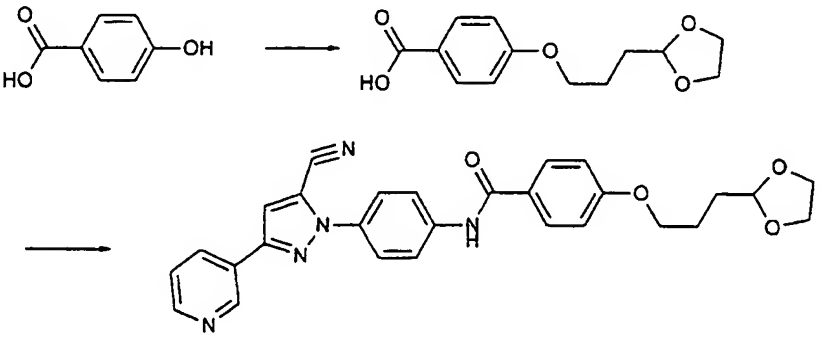
2-Hydroxynicotinic acid (72 mmol) was added to a solution of thionyl chloride (30 mmol) in MeOH (150 mL), cooled to 0°C. The reaction mixture was stirred at room temperature for 2 days but most solids did not dissolve. Sulfuric acid (concentrated, 5 mL) was added, and the reaction stirred at reflux overnight. Volatiles were removed and the residue was treated with ice. The solid product (6-hydroxynicotinic acid, methyl ester) was collected by filtration, washed with water and dried. Additional product was isolated upon concentration of aqueous washes. The combined product (8 g, 73%) was taken on without further purification

To a stirred solution of this ester (10 mmol) in DMF (30 mL), was added cesium carbonate (10 mmol), After 30 minutes, 4-bromobutyronitrile (10 mmol) was added and the reaction mixture was heated at 65°C on an oil bath. After 1.5 hours, the mixture was cooled to room temperature, volatiles were removed, the residue was taken up in water and extracted with dichloromethane. The organic phase was dried over magnesium sulfate and concentrated. Chromatography over silica gel (eluent, dichloromethane/ethyl acetate, 9:1) gave 6-(3-cyanopropyloxy)nicotinic acid, methyl ester (416 mg, 19%) as the faster eluting product. *N*-Alkylated material, 1.5 g (68%), was also obtained.

6-(3-cyanopropyloxy)nicotinic acid, methyl ester (1.8 mmol) was dissolved in methanol/water (16 mL:4 mL) and treated with LiOH monohydrate (2.7 mmol). After stirring overnight, volatiles were removed and reaction neutralized with 1N sulfuric acid. The solid product was collected by filtration, washed with water and dried to give 6-(3-cyanopropyloxy)nicotinic acid (315 mg, 85%).

6-(3-cyanopropyloxy)nicotinic acid (0.6 mmol) was coupled with 3-(3-pyridyl)-5-cyano-1-(4'-aminophenyl)-pyrazole (0.5 mmol) under standard EDC mediated conditions (Method A). Standard work-up gave the title compound (142 mg, 62%), m.p. 190-191°C. ^{1}H NMR($CDCl_3$): δ 2.04-2.11(m, 2 H), 2.67-2.70(7, J=7.1 Hz, 2 H), 4.42-4.45(t, J=6.2 Hz, 2 H), 6.98-7.00(d, J=8.7 Hz, 1 H), 7.53-7.56(m, 1 H), 7.82-7.84(d, J=8.9 Hz, 2 H), 8.02-8.04(d, J=8.9 Hz, 2 H), 8.1(s, 1 H), 8.28-8.32(m, 2 H), 8.63-8.64(m, 1 H),8.82-8.83(m, 1 H), 9.15-9.16(m, 1 H), 10.6(s, 1 H).

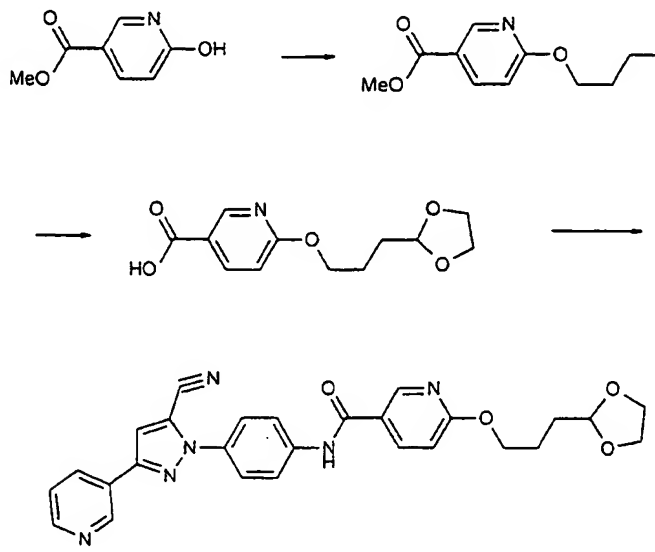
Example 27: Synthesis of 4-[(3-[1,3]dioxolan-2-yl-propoxy)]-N-[4-(5-cyano-3-pyridin-3-yl-pyrazol-1-yl)phenyl]benzamide



4-Hydroxybenzoic acid (22 mmol) was dissolved in absolute EtOH (120 mL) and treated with solid NaOEt (46 mmol). After stirring for 15 minutes. 2-(3-chloropropyl)-1,3-dioxolane (20 mmol) was added and the reaction mixture was heated overnight at 90 °C in an oil bath. An additional 40 mmol of 2-(3-chloropropyl)-1,3-dioxolane was added and the reaction was refluxed overnight. After letting the reaction mixture cool to room temperature, volatiles were removed, the residue was taken up in ice and the mixture was adjusted to pH 6 with 1N sulfuric acid. Solids were collected by vacuum filtration, washed with water and dried. Crude solids were taken up in warm hexanes, filtered and dried to give the acid (2.35 g, 46%) which was taken on without any further purification.

The acid from above (0.75 mmol) was coupled with 3-(3-pyridyl)-5-cyano-1-(4'-aminophenyl)-pyrazole (0.5 mmol) under standard EDC mediated conditions. Crude product was recrystallized from hot benzene /methanol solution m.p. 192-193°C. ^{1}H NMR($CDCl_3$): δ 1.72-1.76(m, 2 H), 1.77-1.86(m, 2 H), 3.77-3.83(m, 2 H), 3.86-3.92(m, 2 H), 4.09-4.12(t, J=6.2 Hz, 2 H), 4.86-4.88(t, J=4.6 Hz, 1 H), 7.08-7.10(d, J=8.7 Hz, 2 H), 7.53-7.56(m, 1 H), 7.79-7.81(d, J=8.8 Hz, 2 H), 7.98-8.00(d, J=8.7 Hz, 2 H), 8.03-8.05(d, J=8.9 Hz, 2 H), 8.1(s, 1 H), 8.30-8.32(d, J=8 Hz, 1 H), 8.63-8.64(d, J=4.4 Hz, 1 H), 9.15(s, 1 H), 10.4(s, 1 H).

Example 28: Synthesis of 6-[(3-[1,3]dioxolan-2-yl-propoxy)]-N-[4-(5-cyano-3-pyridin-3-yl-pyrazol-1-yl)phenyl]nicotinamide



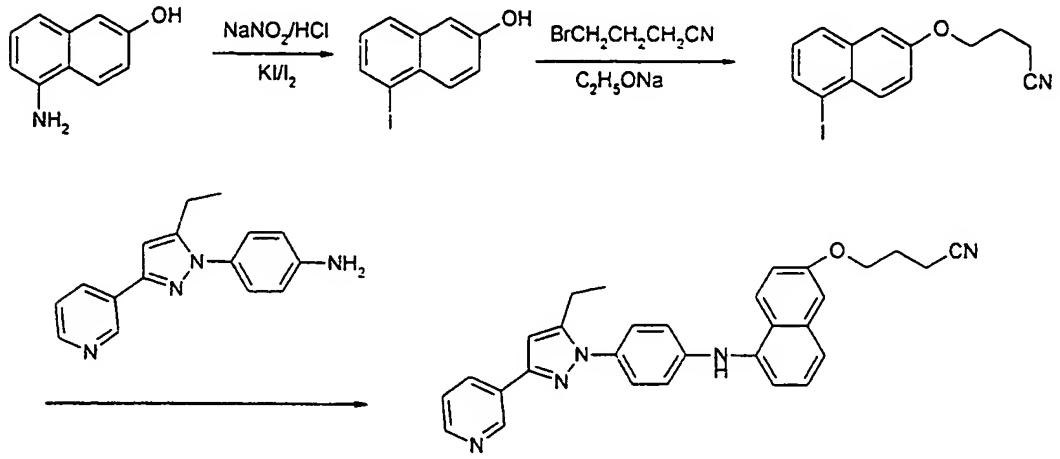
To a stirred solution of 6-hydroxynicotinic acid methyl ester (prepared as describrd in Example 25) (10 mmol) in DMF (30 mL) was added cesium carbonate (10 mmol). After 30 minutes, 2-(3-chloropropyl)-1,3-dioxolane (10 mmol) was added and the reaction mixture was heated at 65°C on an oil bath. After 2 days, the mixture was cooled to room temperature, volatiles were removed, the residue was taken up in water, and extracted with dichloromethane. The organic phase was dried over magnesium sulfate and concentrated. Chromatography of the residue over silica gel (eluent dichloromethane/ethyl acetate 9:1) gave the desired product as the faster eluting product (311 mg, 12%).

This ester (1.1 mmol) was dissolved in methanol/water (8 mL:2 mL) and treated with LiOH monohydrate (1.7 mmol). After stirring overnight, volatiles were removed, and the mixture was neutralized with 1N sulfuric acid. The solid product was collected by filtration, washed with water and dried to give the free carboxylic acid (250 mg, 87%).

The carboxylic acid (0.46 mmol) was coupled with 3-(3-pyridyl)-5-cyano-1-(4'-aminophenyl)-pyrazole (0.38 mmol) under standard EDC mediated conditions (Method A) to give the title compound (118 mg, 63%) m.p. 197-198°C. ^{1}H NMR($CDCl_3$): δ 1.70-1.75(m,

2H), 1.80-1.86(m, 2 H), 3.76-3.82(m,2 H), 3.85-3.92(m, 2 H), 4.37-4.40(t, J=6.4 Hz, 2 H), 4.85-4.87(t, J=4.5 Hz, 1 H), 6.96-6.99(d, J=8.7 Hz, 1 H), 7.53-7.56(m, 1 H), 7.81-7.84(d, J=8.9 Hz, 2 H), 8.01-8.04(d, J=8.9 Hz, 2 H), 8.1(s, 1 H), 8.25-8.32(m, 2 H), 8.63-8.64(m, 1 H),8.81-8.82(m, 1 H), 9.15-9.16(m, 1 H), 10.6(s, 1 H).

Example 29: Synthesis of 6-[(3-cyanopropoxy)napthalen-1-yl]-[4-(5-ethyl-3-pyridin-3-yl-pyrazol-1-yl)phenyl]amine



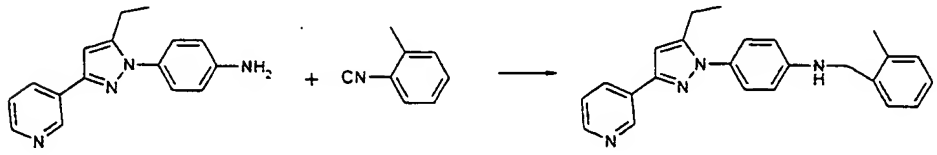
To a stirred mixture of 5-amino-2-naphthol (2.5 g, 15.7 mmol) in 17 % HCl (50 mL) was added a solution of $NaNO_2$ (2.1 g, 30.4 mmol) in water (20 mL) at 0 °C. After 15 minutes, a solution of urea (2.5 g, 41.6 mmol) in water (20 mL) was added and the mixture was stirred for 15 minutes. The reaction mixture was filtered and the filtrate was added to a solution of KI (18.0 g, 108.4 mmol) and I_2 (5.0 g, 197.0 mmol) in water (30 mL) warmed to 70 °C. The mixture was cooled overnight in the refrigerator. The black precipitate was filtered and treated with 10 % Na_2SO_4 (35 mL) for 10 min. Then a solution of 1 N NaOH (60 mL) was added, and the pH was adjusted to 6.5 with 36 % HCl. Filtration gave 5-iodo-2-naphthol (0.60 g, 14.2 %).

To a stirred mixture of 5-iodo-2-naphthol (300 mg, 1.11 mmol) in EtOH (7 mL) was added $NaOC_2H_5$ (90.7 mg, 1.2 equiv) and, after 10 min, 4-bromobutyronitrile (0.22 mL, 2.0 equiv). The mixture was then heated at reflux for 2 h. It was diluted with water, extracted with dichloromethane, washed with brine and dried (Na_2SO_4). Concentration and chromatography

on silica gel (hexane/ethyl acetate = 4:1) gave 1-(cyanopropyloxy)-5-iodonaphthalene (77 mg, 20.6 %).

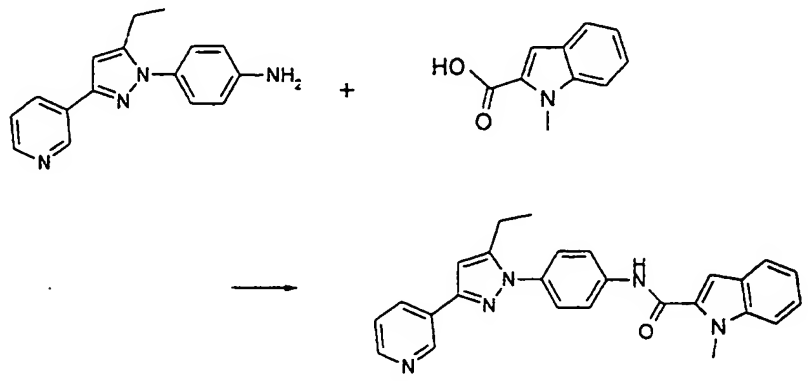
A mixture of 2-(3-cyanopropoxy)-5-iodonaphthalene (77.0 mg, 0.228 mmol), with 5-ethyl-3-(3-pyridyl)-1-(4'-aminophenyl)pyrazole (72.4 mg, 1.2 equiv.), NaO-*t*-Bu (40.8 mg, 1.86 equiv.), $Pd_2(dba)_3$ (5.2 mg, 2.5 % equiv.) and (-)BINAP (10.6 mg, 7.5 % equiv.) in toluene (1 mL) was heated at 80 °C for 18 h. The mixture was diluted with ethyl acetate, filtered through diatomaceous earth and concentrated. Chromatography on silica gel gave the title compound (98.0 mg, 90.8 %). ^{1}H-NMR ($CDCl_3$): 1.30 (t, J = 7.4 Hz, 3 H), 2.20-2.25 (m, 2 H), 2.62-2.74 (m, 4 H), 4.22 (t, J = 5.4 Hz, 2 H), 6.31 (bs, 1 H), 6.59 (s, 1 H), 6.99 (d, J = 8.6 Hz, 2 H), 7.17 (d, J = 9.1 Hz, 1 H), 7.20 (s, 1 H), 7.29-7.34 (m, 4 H), 7.43 (t, J = 8.0 Hz, 1 H), 7.56 (d, J = 8.2 Hz, 1 H), 7.98 (d, J = 9.2 Hz, 1 H), 8.21 (d, J = 7.9 Hz, 1 H), 8.56 (d, J = 4.2 Hz, 1 H), 9.11 (s, 1 H).

Example 30: Synthesis of [4-(5-ethyl-3-pyridin-3-yl-pyrazol-1-yl)phenyl]-(2-methylbenzyl)amine



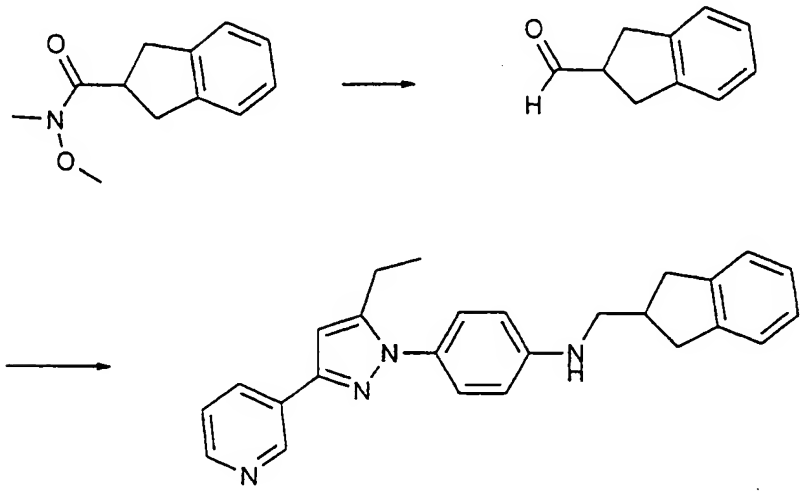
A slurry of Raney Ni (200 mg, 50 % in water) was added to a solution 5-ethyl-3-(3-pyridyl)-1-(4'-aminophenyl)pyrazole (500 mg, 1.89 mmol) and *o*-tolunitrile (0.27 mL, 1.2 equiv.) in glacial acetic acid (20 mL), and the mixture was stirred under hydrogen at 40 psi for 7.5 h. The reaction mixture was filtered through diatomaceous earth, diluted with water, extracted with ethyl acetate, washed with brine, dried (Na_2SO_4) and concentrated. Chromatography on silica gel (hexane/ethyl acetate = 1:1) gave the title compound (595 mg, 85 %). ^{1}H-NMR ($CDCl_3$): 1.30 (t, J = 7.5 Hz, 3 H), 2.42 (s, 3 H), 2.69 (q, J = 7.5 Hz, 2 H), 3.95-4.25 (bs, 1 H), 4.36 (s, 2 H), 6.58 (s, 1 H), 6.72 (d, J = 8.7 Hz, 1 H), 7.21-7.41 (m, 6 H), 8.21 (dd, J = 1.6, 6.3 Hz, 1 H), 8.56 (d, J = 4.1 Hz, 1 H), 9.10 (d, J = 1.6 Hz, 1 H).

Example 31: Synthesis of N-[4-(5-Ethyl-3-pyridin-3-yl-pyrazol-1-yl)phenyl]-1-methylindole-2-carboxamide



A DMF (2mL) solution of 3-(3-pyridyl)-5-ethyl-1-(4'-aminophenyl)pyrazole (264mg, 1 mmol), N-methylindole -2- carboxylic acid (192.5mg, 1.1mmol), PyBOP (570mg, 1.1mmol) and N,N-diisopropylethylamine (0.21mL, 1.2mmol) was stirred at room temperature. for 18hr. The reaction mixture was poured into crushed ice, and extracted with methylene chloride (3 X 50mL). The combined extracts were washed with water, dried over anhydrous sodium sulfate, and the solvent was evaporated. Chromatography of the residue over silica gel (4% methanol/methylene chloride) followed by preparative TLC (silica gel, developer 5% methanol/methylene chloride) gave the title compound as a light, cream colored solid, m.p. 178-179 °C. ^{1}H NMR (DMSO-d6) δ 1.2 (3H, t, J=7.5), 2.73 (2H, q, J = 7.5 Hz), 4.05 (3H, s), 6.93 (1H, s), 7.16 (1H, t, J=7.5), 7.34 (1H, t, J=7.5), 7.37 (1H, s), 7.44-7.48 (1H, dd, J = 3.1 & 4.7 Hz), 7.57-7.61 (3H, m), 7.74 (1H, d, J = 7.9 Hz), 7.98 (2H, d, J = 8.8 Hz), 8.2-8.22 (1H, m), 8.53-8.54 (1H, m), 9.07 (1H, d, J = 1.8 Hz), 10.56 (1H, s).

Example 32: Synthesis of [4-(5-ethyl-3-pyridin-3-yl-pyrazol-1-yl)phenyl]-(2-indanylmethyl)amine

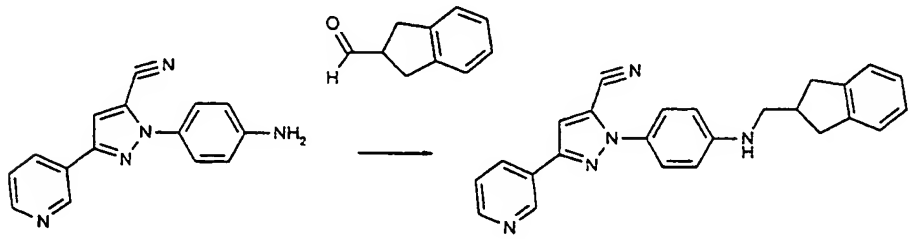


A solution of indane 2-carboxylic acid (324 mg, 2 mmol) and carbonyldiimidazole (299 mg, 2.2 mmol) in DMF (5 mL) was stirred at room temperature for 30 min. N,N-diisopropylethylamine (0.522 mL, 3 mmol) was added followed by N-methoxymethyl amine hydrochloride (195 mg, 2 mmol). The reaction mixture was stirred at room temperature for 18 h, and then treated with 1N sulfuric acid (100 mL). The mixture was extracted with methylene chloride (3 X 50 mL), and the combined extracts were washed with water, dried over anhydrous sodium sulfate, and evaporated to give N-methoxy-N-methyl-indane-2-carboxamide as a light brownish oil which was used without further purification in the next step.

To a stirred ice-cold solution of the above amide (400 mg, 1.9 mmol) in ether (20 mL), was added lithium aluminium hydride (1 M in THF, 4 mL). After stirring the ice-cold mixture for 1h, excess reducing agent was quenched by the careful addition of 1N sulfuric acid (10mL). The reaction mixture was stirred for 5min, the ether layer was decanted and the remaining solid was washed with ether (100 mL). The combined ether extract was washed with water, dried over anhydrous sodium sulfate, and evaporated to give indane 2-carboxaldehyde as a light brownish oil which was used without further purification in the next step.

A solution of 3-(3-pyridyl)-5-ethyl-1-(4'-aminophenyl)pyrazole (185 mg, 0.7 mmol) and indane 2-carboxaldehyde (0.96 mmol, 140 mg) in methanol (9 mL) and acetic acid (1 mL) was stirred at room temperature for 30 min. Sodium cyanoborohydride (124 mg, 2 mmol) was added and stirring continued at room temperature. After 3 h the solvent was evaporated under vacuum, the residue was taken up in sodium bicarbonate solution (50mL), and extracted with methylene chloride (3 X 50mL). The combined organic extracts were washed with water, dried over anhydrous sodium sulfate, and evaporated. Chromatography of the residue over silica gel (eluant, 35% ethyl acetate in methylene chloride) gave the title compound which was taken up in 50% aqueous acetonitrile containing 1% trifluoroacetic acid and lyophilized to give a light yellow solid. ^{1}H NMR (DMSO-d_6) δ 1.2 (3H, t, J=7.5 Hz), 2.63 (2H, q, J = 7.5 Hz), 2.7-2.76 (3H, m), 3.05-3.12 (4H, m), 6.71 (2H, d, J = 8.7 Hz), 6.98 (1H, s), 7.12-7.14 (2H, m), 7.21-7.24 (4H, m), 7.84-7.88 (1H, m), 8.65 (1H, br. d, J = 8.2 Hz), 8.71 (1H, d, J = 5.1), 9.2 (1H, s).

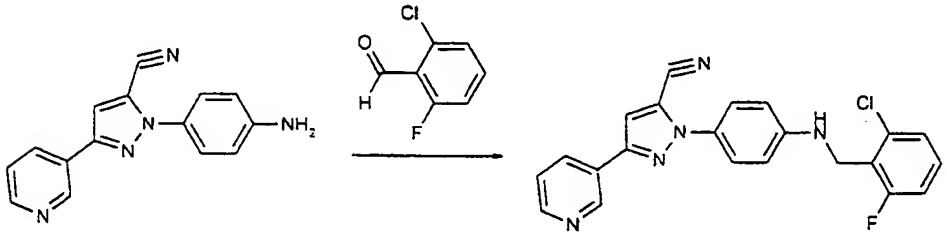
Example 33: Synthesis of [4-(5-cyano-3-pyridin-3-yl-pyrazol-1-yl)phenyl]-(2-indanylmethyl)amine



A solution of 5-cyano-3-(3-pyridyl)-1-(4'-aminophenyl)pyrazole (185 mg, 0.7 mmol) and indane 2-carboxaldehyde (0.96 mmol, 140 mg) in methanol (9 mL) and acetic acid (1 mL) was stirred at room temp for 30 min. Sodium cyanoborohydride (124 mg, 2 mmol) was added and stirring continued at room temperature. After 3 h the solvent was evaporated under vacuum, and the residue was taken up in sodium bicarbonate solution (50 mL) and extracted with methylene chloride (3 X 50 mL). The combined extract was washed with water, dried over anhydrous sodium sulfate and evaporated. Chromatography of the residue over silica gel (eluant.15% ethyl acetate in methylene chloride) gave the title compound as a

cream colored solid, m.p. 156-158 °C. ^{1}H NMR (DMSO-d6): δ 2.68-2.82 (3H, m), 3.05-3.15 (4H, m), 6.36-6.42 (1H, br. t), 6.75-6.77 (2H, d, J = 8.9 Hz), 7.09-7.15 (2H, m), 7.21-7.24 (4H, m), 7.45-7.47 (2H, d, J = 8.8 Hz), 7.51-7.54 (1H, m), 7.98 (1H, s), 8.21-8.28 (1H, br. d.), 8.6-8.62 (1H, br. d.), 9.1 (1H, d, J = 1.9 Hz).

Example 34: Synthesis of (2-Chloro-6-fluorobenzyl)-[4-(5-cyano-3-pyridin-3-yl-pyrazol-1-yl)phenyl]amine



To a stirred solution of 1-(4-aminophenyl)-3-(3-pyridyl)-5-cyanopyrazole (130 mg, 0.5 mmol) in acetic acid (2 mL) and MeOH (6 mL) at room temperature was added 2-chloro-6-fluorobenzaldehyde (79 mg, 0.5 mmol), followed by sodium cyanoborohydride (79 mg, 1.25 mmol). The reaction mixture was stirred at room temperature for 16 h and then concentrated under a stream of nitrogen. The residue was diluted with water, extracted into ethyl acetate, washed with sodium bicarbonate solution and water, and dried ($MgSO_4$). The residue obtained on concentration was flash chromatographed on silica gel (eluent, gradient of 20-30% EtOAc in CH_2Cl_2) to provide the title compound (103 mg, 51%). NMR ($CDCl_3$, 400MHz): 9.1 (s, 1H); 8.7(br, 1H); 8.3(d, 1H); 7.6-7.5(overlapping m, 3H), 7.6-7.5(overlapping m, 4H), 7.05(m,1H); 6.9(d,2H), 4.6(s,2H).

Example 35: Synthesis of [4-(5-Cyano-3-pyridin-3-yl-pyrazol-1-yl)phenyl]-(2,6-dimethylbenzyl)-amine

To a stirred solution of 2,6-dimethylbenzonitrile (1 g, 7.6 mmol) in THF (15 mL) under argon at 0^0 C a solution of DIBAL (1 M in THF, 8 mL, 8 mmol) was added dropwise over 5 minutes. After 3 hr at 0^0 C, the reaction mixture was brought to room temperature and stirred overnight. The reaction was quenched with 5% sulfuric acid at 0^0 C, extracted with ether, washed with brine and dried ($MgSO_4$). Concentration provided 2,6-dimethylbenzaldehyde (0.9 g) which was used without further purification.

To a stirred solution of 1-(4-aminophenyl)-3-(3-pyridyl)-5-cyanopyrazole (130 mg, 0.5 mmol) and 2,6-dimethylbenzaldehyde (0.9 g) in acetic acid (2 mL) and MeOH (5 mL) at room temperature was added sodium cyanoborohydride (79 mg, 1.25 mmol). The reaction mixture was stirred at room temperature for 18 hr and then concentrated under a stream of nitrogen, diluted with water, extracted into ethyl acetate, washed with sodium bicarbonate solution, water and dried ($MgSO_4$). The residue obtained on concentration was flash chromatographed on silica gel (elution with a gradient of 15-25% EtOAc in CH_2Cl_2) providing the title compound (142 mg, 75%). NMR ($CDCl_3$, 400MHz): 9.1 (s, 1H); 8.7(br, 1H); 8.3(d, 1H); 7.6(d, 2H), 7.5(m, 1H), 7.35(s,1H); 7.2(m,1H), 7.1 (overlapping m, 2H), 6.8 (d,2H), 4.3 (s,2H), 2.4(s,6H).

Example 36: Synthesis of [4-(5-Cyano-3-pyridin-3-yl-pyrazol-1-yl)phenyl]-(2-chloro-6-methylbenzyl) amine

To a stirred solution of 2-chloro-6-methylbenzonitrile (1 g, 6.6 mmol) in THF (15 mL) under argon at 0^0 C a solution of DIBAL (1 M in THF, 7mL, 7 mmol) was added dropwise over 5 minutes. After 3 hr at 0^0 C, the reaction mixture was brought to room temperature and further stirred overnight. The reaction mixture was quenched with 5% sulfuric acid at 0^0 C, extracted with ether, washed with brine and dried ($MgSO_4$). Concentration provided 2-chloro-6-methylbenzaldehyde (0.92 g) which was used without further purification.

To a stirred solution of 1-(4-aminophenyl)-3-(3-pyridyl)-5-cyanopyrazole (130 mg, 0.5 mmol) and 2-chloro-6-methylbenzaldehyde (0.9 g) in acetic acid (4 mL) and MeOH (7 mL)

at room temperature was added sodium cyanoborohydride (79 mg, 1.25 mmol). The reaction mixture was stirred at room temperature for 16 h and then concentrated under a stream of nitrogen, diluted with water, extracted into ethyl acetate, washed with sodium bicarbonate solution, water and dried ($MgSO_4$). The residue obtained on concentration was chromatographed on silica gel (eluant, gradient of 15-25% EtOAc in CH_2Cl_2) to provide the title compound (152 mg, 76%). NMR ($CDCl_3$, 400MHz): 9.2 (s, 1H); 8.7(br, 1H); 8.4(br, 1H); 7.6 –7.5 (overlapping m, 3H), 7.4-7.1(overlapping m, 5H), 6.8 (d,2H), 4.5 (s,2H), 2.5(s, 3H).

Example 37: Synthesis of [4-(5-Ethyl-3-pyridin-3-yl-pyrazol-1-yl)phenyl]-(2-chloro-6-fluorobenzyl) amine

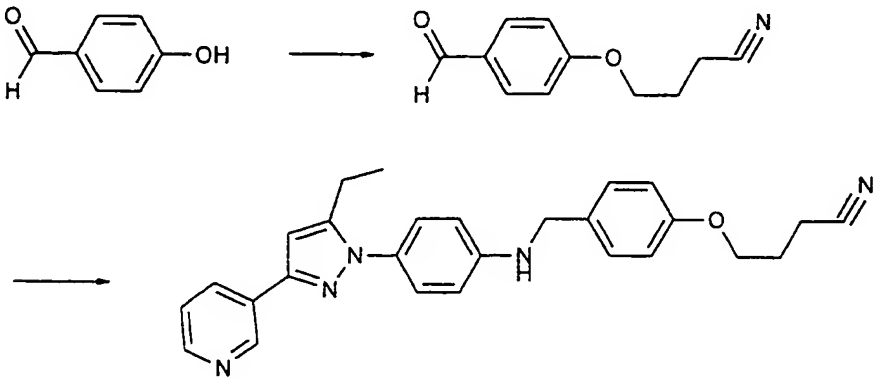
To a stirred solution of 1-(4-aminophenyl)-3-(3-pyridyl)-5-ethylpyrazole (300 mg, 1.14 mmol) and 2-chloro-6-fluorobenzaldehyde (360 mg, 2.27 mmol) in 5% HOAc/MeOH (6 mL) at room temperature under argon was added sodium cyanoborohydride (180 mg, 2.86 mmol). The reaction mixture was stirred at room temperature for 4 h and then concentrated, diluted with water, extracted into ethyl acetate and washed with brine. The residue obtained on concentration was chromatographed on silica gel (eluant, gradient of 25-50% EtOAc in hexane) to provide the title compound as an oil which solidified on trituration with ether /petroleum (152 mg, 32%). m.p. 123-5^0 C. NMR ($CDCl_3$, 400MHz): 9.1 (s, 1H); 8.6(br, 1H); 8.2(br, 1H); 7.4 –7.2 (overlapping m, 5H), 7.05(m, 1H), 6.8 (d,2H),6.6 (s,1H), 4.6 (s,2H), 4.4(br, 1 H), 2.7(q, 2H), 1.2 (t, 3H).

Example 38: Synthesis of [4-(5-Ethyl-3-pyridin-3-yl-pyrazol-1-yl)phenyl]-(2-methylbenzyl)-amine

To a stirred solution of 1-(4-aminophenyl)-3-(3-pyridyl)-5-ethylpyrazole (300 mg, 1.14 mmol) and o-tolualdehyde (260 mg, 2.25 mmol) in 5% HOAc/MeOH (6 mL) at room temperature under argon, sodium cyanoborohydride (200 mg, 3.18 mmol) was added. The reaction mixture was stirred at room temperature for 4 h and then concentrated, diluted with water, extracted into ethyl acetate, washed with brine. The residue obtained on concentration was chromatographed on silica gel (eluant, gradient of 25-50% EtOAc in hexane) to provide the title compound as an oil that solidified on trituration with ether / petroleum ether (97 mg, 23%), m.p. 117-9^0 C. NMR ($CDCl_3$, 400MHz):

9.1 (s, 1H); 8.5(br, 1H); 8.1(br, 1H); 7.4 –7.2 (overlapping m, 7H), 6.7 (d,2H),6.5 (s,1H), 4.4 (s,2H), 4.1(br, 1 H), 2.7(q, 2H), 2.4(s,3H), 1.3 (t, 3H).

Example 39: Synthesis of of [4-(5-Ethyl-3-pyridin-3-yl-pyrazol-1-yl)phenyl]-[4-(3-cyanopropoxy)benzyl]-amine

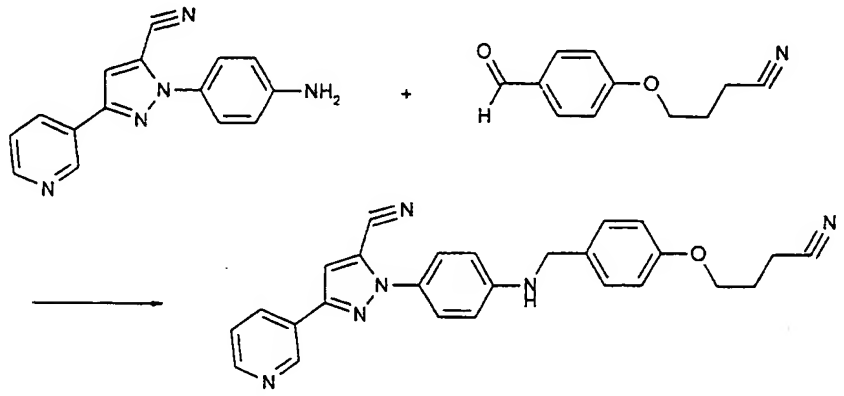


4-Hydroxybenzaldehyde (20 mmol) was dissolved in absolute EtOH (150 mL) and treated with solid NaOEt (24 mmol). After stirring for 15 minutes, 4-bromobutyronitrile (24 mmol) was added and reaction mixture was heated overnight at 90°C in an oil bath. After letting the reaction cool to room temperature, volatiles were removed, the residue was taken up in ice, adjusted to pH 6 with 1N sulfuric acid, and extracted with methylene chloride. The organic phase was washed with brine, dried over $MgSO_4$ and concentrated. Chromatography over silica gel (eluant. 5% EtOAc in hexanes) gave the 4-(3-cyanopropoxy)benzaldehyde (4.8 g, 58%).

3-(3-Pyridyl)-5-ethyl-1-(4'-aminophenyl)-pyrazole (0.5 mmol) was dissolved in MeOH (4 mL) and treated with HOAc (0.5 mL). The reaction was treated with the solution of aldehyde from above (0.75 mmol) in MeOH (1 mL) and stirred at room temperature for 30 minutes. $NaCNBH_3$ (1.25 mmol) was added in one portion. After 2 hrs, volatiles were removed, the residue was taken up in water, neutralized with $NaHCO_3$ (aq) and extracted with dichloromethane. The organic phase was dried over $MgSO_4$ and concentrated. Chromatography over silica gel (eluant, 50% dichloromethane in EtOAc) gave the title compound as an off-white solid (178 mg, 78%), m.p. 131-132°C. ^1H NMR($CDCl_3$): δ 1.15-1.18(t, J=7.5 Hz, 3 H), 1.98-2.04(m, 2 H), 2.56-2.67(m, 4 H), 4.00-4.04(t, J=6 Hz, 2 H), 4.24-

4.26(d, J=5.8 Hz, 2 H), 6.72-6.79(m, 3 H), 6.53-6.56(t, J=5.8 Hz, 1 H), 6.66-6.68(d, J=8.7 Hz, 2 H), 6.80(s, 1 H), 6.92-6.94(d, J=8.4 Hz, 2 H), 7.16-7.18(d, J=8.6 Hz, 2 H), 7.30-7.32(d, J=9.4 Hz, 2 H), 7.40-7.43(m, 1 H), 8.13-8.15(d, J=8 Hz, 1 H), 8.48-8.50(d, J=4.6 Hz, 1 H), 9.0(s, 1 H).

Example 40: Synthesis of [4-(5-cyano-3-pyridin-3-yl-pyrazol-1-yl)phenyl]-[4-(3-cyanopropoxy)benzyl]-amine

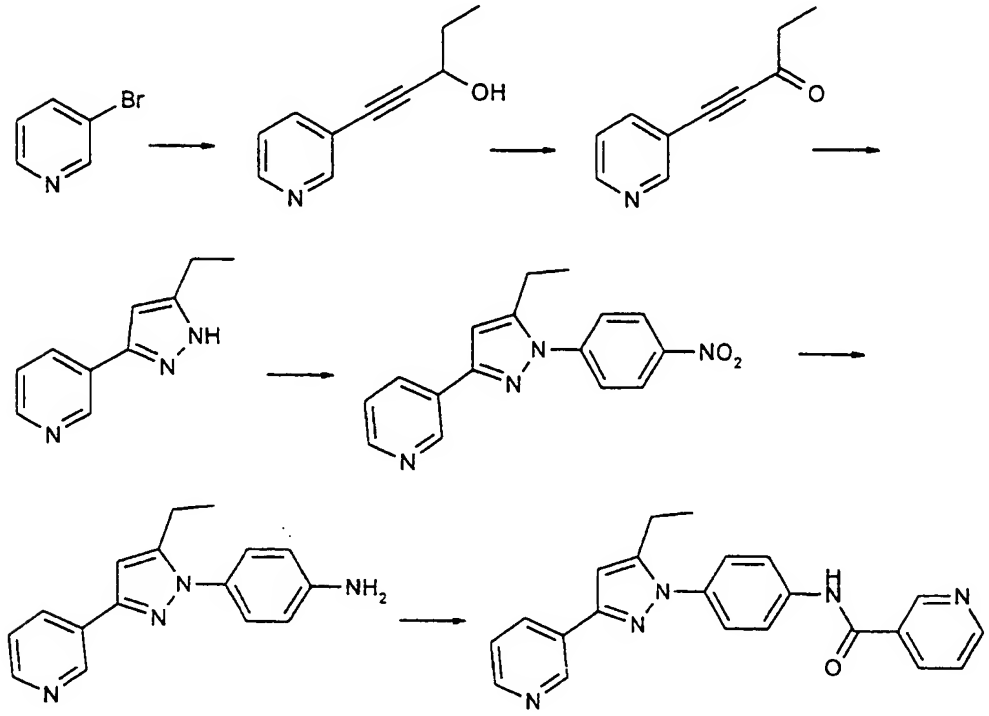


3-(3-Pyridyl)-5-cyano-1-(4'-aminophenyl)pyrazole (0.5 mmol) was dissolved in MeOH (4 mL) and treated with HOAc (4 mL). The reaction was treated with a solution of 4-(3-cyanobutoxy)benzaldehyde (from Example above) (0.75 mmol) in MeOH (1 mL) and stirred at room temperature for 30 minutes. $NaCNBH_3$ (1.25 mmol) was added in one portion. After 2 hr, volatiles were removed, the residue taken up in water, neutralized with $NaHCO_3$ (aq) and extracted with dichloromethane. Organic extracts were combined, dried over $MgSO_4$ and concentrated to leave a clear oil. Pure product was eluted from silica gel column using 50% dichloromethane in EtOAc giving a light yellow solid (140 mg, 64%), m.p. 128-129°C. ^1H NMR($CDCl_3$): δ 1.98-2.04(m, 2 H), 2.63-2.66(t, J=7.1 Hz, 2 H), 4.00-4.04(t, J=6 Hz, 2 H), 4.27-4.29(d, J=5.8 Hz, 2 H), 6.72-6.79(m, 3 H), 6.92-6.94(d, J=8.5 Hz, 2 H), 7.31-7.33(d, J=8.5 Hz, 2 H), 7.42-7.44(d, J=8.7 Hz, 2 H), 7.50-7.53(m, 1 H), 7.96(s, 1 H), 8.24-8.26(d, J=8 Hz, 1 H), 8.60-8.61(d, J=4.6 Hz, 1 H), 9.10(s, 1 H).

Example 41: Synthesis of [4-(5-Ethyl-3-pyridin-3-yl-pyrazol-1-yl)phenyl]-(2-fluoro-6-methylbenzyl) amine

A mixture of 2-chloro-6-methylbenzonitrile (5 g, 33.0 mmol) and CsF (14 g, 92.2 mmol) in DMSO (30 ml) was heated at 140 °C for 15 hr and then allowed to cool to room temperature. It was diluted with water, extracted with dichloromethane, washed with brine, dried (Na_2SO_4) and concentrated to give 2-fluoro-6-methylbenzonitrile (2.93 g, 66 %). A mixture of the above nitrile (250 mg), 1-(4-aminophenyl)-3-(3-pyridyl)-5-ethylpyrazole (200 mg, 0.76 mmol) and Raney Ni (50 % in water, 100 mg) in glacial acetic acid (15 ml) was shaken in a Parr apparatus under H_2 (40 psi) for 7 hr. The catalyst was removed by filtration and the solvent was evaporated. Chromatography on silica gel (hexane/ethyl acetate = 2:1) afforded the title compound (146 mg). ^{1}H-NMR ($CDCl_3$): 1.30 (t, J = 7.5 Hz, 3 H), 2.46 (s, 3 H), 2.67 (q, J = 7.5 Hz, 2 H), 3.92 (bs, 1 H), 4.38 (s, 2 H), 6.58 (s, 1 H), 6.78 (d, J = 8.6 Hz, 2 H), 6.99 (t, J = 6.8 Hz, 1 H), 7.05 (d, J = 7.8 Hz, 1 H), 7.19-7.38 (m, 4 H), 8.20 (d, J = 7.8 Hz, 1 H), 8.56 (d, J = 3.7 Hz, 1 H), 9.10 (s, 1 H).

Example 42: Synthesis of N-[4-(5-Ethyl-3-pyridin-3-yl-pyrazol-1-yl)phenyl]nicotinamide



To a solution of 3-bromopyridine (12.0 g, 75.6 mmol) and 1-pentyn-3-ol (7.0 mL, 83.2 mmol) in triethylamine (150 mL) were added $Pd(PPh_3)_4$ (88 mg, 0.076 mmol) and copper(I) bromide dimethylsulfide (31 mg, 0.15 mmol). The mixture was heated at 70°C for 5 hr, cooled to room temperature and filtered. The filter cake was washed with EtOAc (30 mL). The combined filtrate was concentrated to give 1-(3-pyridinyl)-1-pentyn-3-ol (12.2 g, 99%) as a dark oil.

To a solution of $(COCl)_2$ (7.9 mL, 91.0 mmol) in CH_2Cl_2 (300 mL) was added DMSO (11.0 mL, 151 mmol) at –78°C, followed by 1-(3-pyridinyl)-1-pentyn-3-ol (12.2 g, 75.6 mmol) in CH_2Cl_2 (100 mL). The mixture was stirred at -78°C for 1 hr, and then quenched with triethylamine (32 mL, 227 mmol). After being warmed to 0°C, the mixture was diluted with water and the layers were separated. The organic phase was dried over $MgSO_4$ and concentrated to give 1-(3-pyridinyl)-1-pentyn-3-one (12.2 g, 99%) as an oil. ^1H NMR ($CDCl_3$, 400MHz) 8.81 (bs, 1H), 8.68 (bs, 1H), 7.87 (m, 1H), 7.32 (m, 1H), 2.73 (q, J=7.4Hz, 2H), 1.24 (t, J=7.4Hz, 3H).

To a solution of the above propargyl ketone (12.2 g, 75.6 mmol) in EtOH (200 mL) at room temperature hydrazine monohydrate (4.2 mL, 83.2 mmol) was added over 15 min. The mixture was stirred at room temperature for 3 hr and concentrated. The residue was taken up in EtOAc and washed with water. The organic phase was dried over $MgSO_4$ and concentrated to give 3-(3-pyridinyl)-5-ethylpyrazole (13.2 g, 99%) as a solid. ^{1}H NMR ($CDCl_3$, 400MHz) 9.00 (s, 1H), 8.85 (d, J=4.6Hz, 1H), 8.07 (d, J=7.9Hz, 1H), 7.32 (m, 1H), 6.43 (s, 1H), 2.75 (q, J=7.6Hz, 2H), 1.24 (t, J=7.6Hz, 3H).

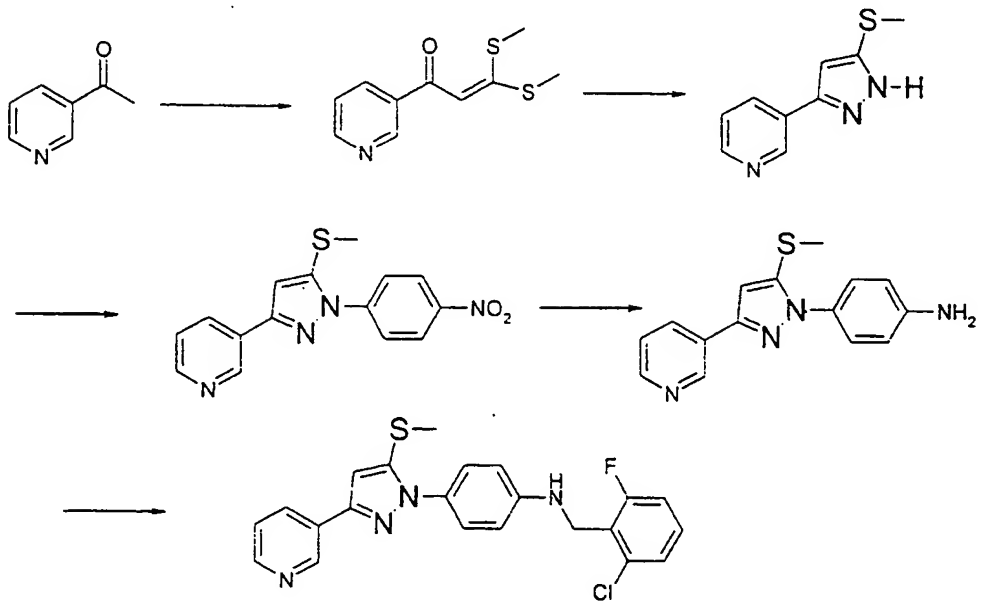
To a solution of 3-(3-pyridinyl)-5-ethylpyrazole (13.2 g, 75.6 mmol) in DMSO (70 mL) was added *t*-BuOK (9.3 g, 83.2 mmol), and then 4-fluoronitrobenzene (8.8 mL, 83.2 mmol). The mixture was heated to 80 °C for 1 hr. After being cooled to room temperature, the mixture was quenched with water (300 mL). The resulting slurry was stirred for 30 min and filtered. The cake was washed with water and dried in oven under house vacuum at 40 °C overnight. The solid was then treated with a 1:2 mixture of ethyl acetate and hexane (150 mL) and the slurry was filtered. The solid was washed with the same solvent system and dried in an oven under house vacuum to give 1-(4-nitrophenyl)-3-(3-pyridinyl)-5-ethylpyrazole (18.5 g, 82%). ^{1}H NMR ($CDCl_3$, 400MHz) 9.09 (s, 1H), 8.60 (d, J=4.0Hz, 1H), 8.38, 7.76 (ABq, J=9.04Hz, 4H), 8.17(m, 1H), 7.36 (m, 1H), 6.67 (s, 1H), 2.84 (q, J=7.5Hz, 2H), 1.36 (t, J=7.5Hz, 3H).

1-(4-Nitrophenyl)-3-(3-pyridinyl)-5-ethylpyrazole (18.0 g, 61.2 mmol) was dissolved in dioxane (200 mL) and MeOH (200 mL). The solution was treated with ammonium formate (38.6 g, 612 mmol) and 5% Pd/C (1.8 g) at room temperature for 6 hr. It was then filtered through a pad of diatomaceous earth and the cake was washed with CH_3CN. The filtrate was concentrated and the residue was treated with water (200 mL). The resulting slurry was stirred at room temperature for 3 hr, and collected by filtration. The solid was washed with water and dried in an oven under house vacuum to give 1-(4-aminophenyl)-3-(3-pyridinyl)-5-ethylpyrazole (15.5 g, 95%). %). ^{1}H NMR ($CDCl_3$, 400MHz) 9.05 (s, 1H), 8.53 (d, J=4.7Hz, 1H), 8.16(d, J=7.2Hz, 1H), 7.30 (m, 1H), 7.23, 6.75 (ABq, J=8.1Hz, 4H) 6.54 (s, 1H), 3.83 (bs, 2H), 2.63 (q, J=7.6Hz, 2H), 1.25 (t, J=7.6Hz, 3H).

The pyrazole from above (16.2 g, 61.3 mmol) was dissolved in 1:1 mixture of THF and CH_2Cl_2 (300 mL), and nicotinic acid (8.3 g, 67.4 mmol) and EDC (14.1 g, 73.5 mmol) were

added. The resulting mixture was stirred at room temperature for 5 hr. The resulting solution was concentrated and the residue was treated with water (300 mL). The slurry was stirred for 2 hr and then filtered. The cake was washed with water, dried in an oven at 40 °C under house vacuum overnight. The dried solid (22.6 g) was recrystallized from an 8:1 mixture of EtOAc and MeOH to give the title compound (20.5 g, 91%), m.p. 188-190 °C. 1H NMR ($CDCl_3$, 400MHz): 9.13 (s, 1H), 9.06(s, 1H), 8.79(d, J=4.8Hz, 1H), 8.53(d, J=4.6Hz, 1H), 8.31 (s, 1H, NH), 8.17(m, 1H), 8.15(m, 1H), 7.80, 7.51(ABq, J=7.2Hz, 4H), 7.50(m, 1H), 7.26(m, 1H), 6.59(s, 1H), 2.73(q, J=7.4Hz, 2H), 1.29(t, J=7.4Hz, 3H).

Example 43: Synthesis of [4-(5-Methylthio-3-pyridin-3-yl-pyrazol-1-yl)phenyl]-(2-chloro-6-fluorobenzyl)amine.



A mixture of 3-acetylpyridine (5g, 41.2 mmol), sodium hydride (60%, 0.3.g, 82.5 mmol), carbon disulfide (3.72 mL, 61.9mmol) and methyl iodide (7.71 mL, 123.8 mmol) in dry benzene (70 mL) was stirred at 0 °C in an ice-bath under argon atmosphere. Dimethylacetamide (8 mL) was carefully added which initiated a vigorous reaction. The reaction mixture was further stirred for 1 h. The reaction mixture was diluted with ice-water, the aqueous layer was extracted with ethyl acetate and the combined organic extracts were

washed with water and dried ($MgSO_4$). The resulting dimethylthiovinyl ketone (5.2 g) was used directly in the next step.

A mixture of the above ketone (4.2 g, 41.2 mmol) and hydrazine hydrate (1 mL, 20.5 mmol) in EtOH (50 mL) was refluxed for 14 h. The reaction mixture was concentrated, diluted with water, extracted with ethyl acetate, the combined organic extracts were washed with water and dried ($MgSO_4$). The crude solid obtained on concentration was recrystallized from EtOAc/hexane to give 5-methylthio-3-(3-pyridinyl)pyrazole (2.0g).

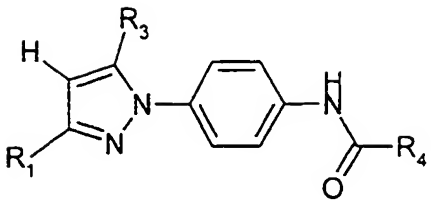
A solution of the above pyrazole(1.94 g, 10.15 mmol) and potassium t-butoxide (1.2 g, 10.6 mmol) in anhydrous DMSO (15 mL) was stirred at room temperature for 5 min and then 4-flouronitrobenzene (1.08 mL, 10.15 mmol) was added. The reaction mixture was heated to 100 ^{0}C in an oil bath for 5 h under argon. The reaction mixture was cooled, diluted with water, the yellow solid obtained was filtered, washed with water and dried. The residue obtained was recrystallized from ethyl acetate to give 5-methylthio-1-(4-nitrophenyl)-3-(3-pyridinyl)pyrazole (2.4 g).

To a stirred suspension of the above nitro compound (1.2 g, 3.85 mmol) in glacial acetic acid (40 mL) was added a solution of $SnCl_2.2H_2O$ (6.07 g, 26.9 mmol) in conc. HCl (10 mL) and the reaction was stirred overnight at room temperature. The reaction mixture was diluted with water and brought to pH ~12 by the addition of 5N KOH solution, extracted with EtOAc. The organic layer was washed with water (4X), dried over $MgSO_4$ and concentration to give the corresponding amine (0.7 g).

A solution of the above amine (100 mg, 0.35 mmol) and 2-chloro-6-fluorobenzaldehyde (56 mg, 0.35 mmol) in acetic acid (0.5 mL) and MeOH (4 mL) was stirred at room temperature. Sodium cyanoborohydride (56 mg, 0.88 mmol) was added and the reaction mixture was stirred an additional 24 hr at room temperature. The reaction mixture was concentrated, diluted with EtOAc, washed with water and $NaHCO_3$ solution, and dried ($MgSO_4$). The residue obtained on concentration was flash chromatographed on silica gel to give the title compound (55 mg).

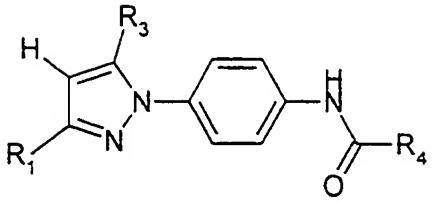
Using Methods analogous to those described above. the following compounds of this invention (Tables 1-6) were prepared.

TABLE 1



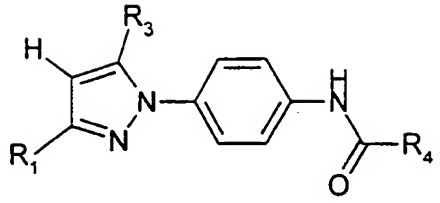
Cpd. #	R_1	R_3	R_4	m.p. °C
529	CF_3	CF_3	2-ClPh	179.5-180
532	CF_3	CF_3	2,4-diClPh	153.5-154
533	CF_3	CF_3	2,5-diClPh	165-166
534	CF_3	CF_3	2,3-diClPh	188.5-190
535	CF_3	CF_3	2,6-diClPh	220-220.5
536	CF_3	CF_3	3,4-diClPh	177-178
538	CF_3	CF_3	Ph	243-245
539	CF_3	CF_3	3-ClPh	160-165
542	CF_3	CF_3	3,5-diClPh	209-210
552	CF_3	CF_3	4-MePh	228-230
553	CF_3	CF_3	4-MeOPh	213.5-215
567	CF_3	CF_3	3-MeOPh	189-190
576	CF_3	CF_3	3-MePh	144
577	CF_3	CF_3	2-MeOPh	101-102
581	CF_3	CF_3	3,4-(OCH_2O)Ph	
590	CF_3	CF_3	4-(1-imidazolyl)Ph	
607	CF_3	CF_3	4-Me_2NPh	
C5374	CF_3	CF_3	4-ClPh	
696	CF_3	CF_3	4-MeSPh	224-225
703	CF_3	CF_3	4-MeS(O)Ph	187-188
710	CF_3	CF_3	4-$MeSO_2$Ph	221-222
716	CF_3	CF_3	4-Me_2NCH_2Ph	159-160
719	CF_3	CF_3	2-(H_2NSO_2)Ph	
730	CF_3	CF_3	3-Me_2NPh	181-184
748	CF_3	CF_3	4-CNPh	177-179
755	CF_3	CF_3	2-(NO_2)Ph	
759	CF_3	CF_3	3-$MeSO_2$Ph	209-210
543	CF_3	CF_3	3-Py	163-166
544	CF_3	CF_3	4-Py	163-166
545	CF_3	CF_3	2-Py	167-168
549	CF_3	CF_3	2-Th	232-234
574	CF_3	CF_3	(6-Cl)-3-Py	209-210
575	CF_3	CF_3	(2-Cl)-4-Py	188-190
591	CF_3	CF_3	(2,5-diMe)-2-Thz	

TABLE 1



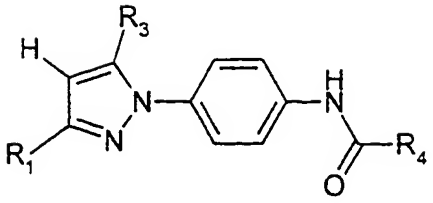
Cpd. #	R_1	R_3	R_4	m.p. °C
597	CF_3	CF_3	(2,5-diMe)-3-Furyl	
669	CF_3	CF_3	(2-Cl)3-Py	155-156
676	CF_3	CF_3	(*S*)-2-Pyrrolidinyl	90-91
687	CF_3	CF_3	(*R*)-2-Pyrrolidinyl	91-92
688	CF_3	CF_3	3-Piperidinyl	231-233
698	CF_3	CF_3	2-Pyrazinyl	188-189
705	CF_3	CF_3	(2,6-diMeO)-3-Py	128.5-130
711	CF_3	CF_3	4-Quinolinyl	204-205
712	CF_3	CF_3	2-Quinoxalinyl	196
723	CF_3	CF_3	(*S*)-2-Pyrrolidinone-5-yl	184-185
725	CF_3	CF_3	3-(N-Me)-Piperidinyl	115-116
726	CF_3	CF_3	N-Morpholinyl	185-186
727	CF_3	CF_3	3-Py(N-oxide)	>275
728	CF_3	CF_3	4-Py(N-oxide)	235-238
731	CF_3	CF_3	(*S*)-3-Tetrahydro-isoquinolinyl	81-85
790	CF_3	CF_3	(2-Cl-5-Br)3Py	182-184
530	CF_3	CF_3	$(CH_2)_2$4ClPh	169.5-171
531	CF_3	CF_3	$CH_2$4-ClPh	168.5-170
546	CF_3	CF_3	$(CH_2)_2$4-(PhC(O))Ph	
547	CF_3	CF_3	Me	175-176
584	CF_3	CF_3	*n*-Pentyl	107-109
660	CF_3	CF_3	$C(Cl)=C(Cl)_2$	
670	CF_3	CF_3	3-(N-Boc)piperidinyl	81-82
673	CF_3	CF_3	$CH_2$4-Py	217-218
713	CF_3	CF_3	CH_2NHPh	142-144
715	CF_3	CF_3	CH_2(2-Pyrrolidinone-N-yl)	168-170
744	CF_3	CF_3	$(CH_2)_2C(O)NH_2$	227-228
749	CF_3	CF_3	CH_2NMe_2	105-107
555	CF_3	Ph	4-ClPh	209-210
561	*t*-Bu	*t*-Bu	4-ClPh	208-209.5
568	Ph	CF_3	4-ClPh	235.5-238

TABLE 1



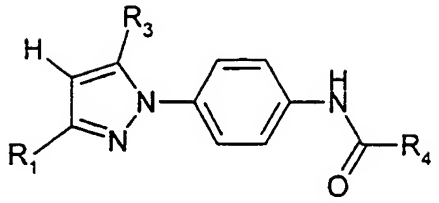
Cpd. #	R_1	R_3	R_4	m.p. °C
571	Me	CF_3	4-ClPh	190-192
572	CF_3	Me	4-ClPh	178-180
602	CF_3	2-Furyl	4-ClPh	223-224
603	2-Furyl	CF_3	4-ClPh	198-199
604	CF_3	Cl	4-ClPh	175-177
628	2-Thienyl	CF_3	4-ClPh	174-174
629	CF_3	2-Thienyl	4-ClPh	258-259
630	*t*-Butyl	CF_3	4-ClPh	
631	CF_3	*t*-Butyl	4-ClPh	
633	CO_2Et	Me	4-ClPh	
649	Me	Ph	4-ClPh	
650	CF_3	CH_2NMe_2	4-ClPh	
652	*t*-Butyl	CF_3	4-ClPh	
661	CF_3	CH_2OH	4-ClPh	
662	CF_3	*i*-Pr	4-ClPh	133-134.5
664	Me	3-Py	4-ClPh	181-184
668	*i*-Pr	CF_3	4-ClPh	201-203
674	2-Furyl	CF_3	3-Py	174-175
677	CF_3	CH_2O-*t*-Bu	4-ClPh	
678	2-Furyl	2-Furyl	4-ClPh	215-217
682	3-Py	CF_3	4-ClPh	238-241
684	*t*-Bu	Me_2N	4-ClPh	
685	CF_3	3-Py	4-ClPh	215-218
686	Me	2-Furyl	4-ClPh	193-194.5
697	Et	CF_3	3-Py	196-198
706	CF_3	Et	3-Py	197-199
707	2-THF	CF_3	3-Py	135-137
708	CF_3	CH_2OMe	4-ClPh	
709	CF_3	CH_2OMe	3-Py	
722	3-Py(N-oxide	CF_3	4-ClPh	143-150
724	CF_3	Me	3-Py	164-166
733	CF_3	2-Oxazolidinyl	3-Py	230-231
736	CF_3	2-Thiazolyl	3-Py	238-240

TABLE 1



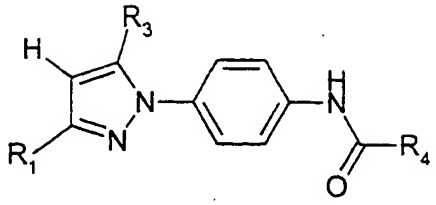
Cpd. #	R_1	R_3	R_4	m.p. °C
737	CF_3	4-Me_2NPh	3-Py	114-116
739	3-Py	CF_3	3-Py	182-184
743	2-Pyrazinyl	Et	3-Py	199-202
746	2-Thiazolyl	CF_3	3-Py	225-227
756	CH_2OMe	Me	4-ClPh	180-181
760	EtO	CF_3	4-ClPh	189-190
761	EtO	CF_3	3-Py	174-175
763	3-Py	CF_3	(5-Br)-3-Py	207-209
768	CF_3	4-Py	3-Py	191-193
776	3-Py	CF_3	(2-Cl)-3-Py	150-151
777	3-Py	CF_3	4-Py	220-221
779	CF_3	Me	4-*t*-BuPh	195-197
780	CF_3	Me	Cyclopentyl	176-178
781	CF_3	Me	3-THF	
782	3-Py	CF_3	4-Imidazolyl	205-210
784	CF_3	CN	4-ClPh	186-187
786	Et	Ph	3-Py	194-195
787	Et	Ph	4-Py	219-221
788	Et	*i*-Pr	4-Py	195-196
789	Et	*i*-Pr	3-Py	194-196
792	CF_3	Me	$(CH_2)_2SO_2Ph$	
793	CF_3	Me	2-Indanyl	
794	CF_3	Me	2-Indolyl	
795	CF_3	Me	$(CH_2)_2$-3-indolyl	
799	*t*-Bu	Me	4-ClPh	203-204
800	*t*-Bu	Me	3-Py	161-163
805	CF_3	Me	CH=CH(3,4-diOMePh)	
807	3-Py	CF_3	(2-MeS)3-Py	205-206
808	*i*-Pr	Ph	3-Py	167-168
813	*i*-Pr	Me	3-Py	149-151
814	Me	*i*-Pr	3-Py	88-90
816	CF_3	Me	4-NO_2Ph	
820	CF_3	Me	*i*-Pr	
821	Et	Et	3-Py	182-184

TABLE 1



Cpd. #	R_1	R_3	R_4	m.p. °C
823	CH_2OMe	CF_3	4-ClPh	173-174
824	CH_2OMe	CF_3	3-Py	134-135
825	3-Py	CF_3	(2-MeSO)3-Py	243-244
826	*i*-Pr	Et	3-Py	178-179
832	CF_3	Me	4-*i*-PrPh	
833	CF_3	Me	4-EtPh	
836	CF_3	Me	(2-Me)3-Py	
837	CF_3	Me	(6-Me)3-Py	
838	CF_3	Me	(2-MeO)3-Py	
843	3-THF	CF_3	4-Py	141-143
844	3-THF	CF_3	(2-MeS-5-Br)4-pyrimidinyl	131-134
845	CF_3	Me	4-CF_3Ph	
846	CF_3	Me	4-CO_2MePh	
847	CF_3	Me	4-*i*-PrOPh	
848	CF_3	Me	(4-Ph)Ph	
850	CF_3	Me	4-n-PentylPh	
852	CF_3	Me	3-Thienyl	
854	CF_3	Me	(3-Me)2-Furyl	
856	CF_3	Me	2-MeCyclohexyl	
857	CF_3	Me	3-MeCyclohexyl	
858	CF_3	Me	4-MeCyclohexyl	
859	CF_3	Me	4-(MeO)Cyclohexyl	
861	CF_3	Me	4-*n*-PentylCyclo-hexyl	
871	CF_3	Me	(2-Me-6-Cl)4-Py	
872	CF_3	Me	4-FPh	
873	CF_3	Me	4-MeC(O)NHPh	
874	CF_3	Me	$CH_2$4-ClPh	
875	CF_3	Me	CH_2(7-Me,N Coumarin-4-yl)	
876	CF_3	Me	N-MePyrrolidin-2-One-4-yl	
878	3-Py	CF_3	(2-OMe)-3-Py	163-4

TABLE 1



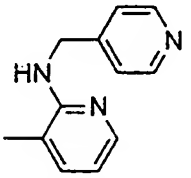
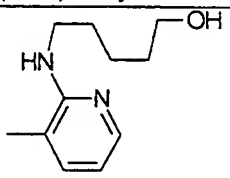
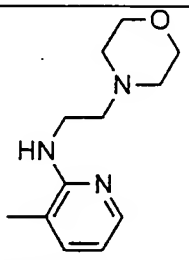
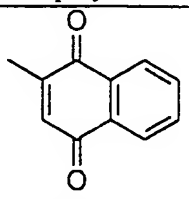
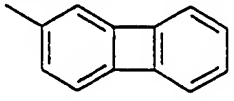
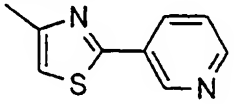
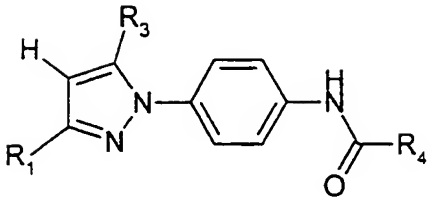
Cpd. #	R_1	R_3	R_4	m.p. °C
879	3-Py	CF_3		107-8
880	3-Py	CF_3	(2-DImethylamino)-3-Py	188-189
881	3-Py	CF_3	(2-Cl)-4-Py	193-194
882	3-Py	CF_3		95-96
883	3-Py	CF_3		85-87
888	CF_3	Me	2-Napthyl	
889	CF_3	Me		
890	CF_3	Me	6-Quinolinyl	
891	CF_3	Me		
892	CF_3	Me	1-Napthyl	
893	CF_3	Me		

TABLE 1



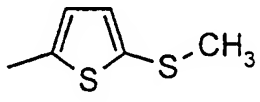
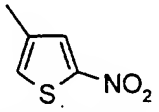
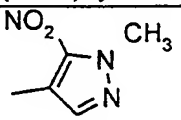
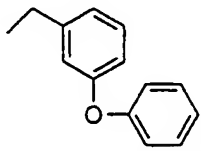
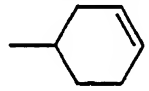
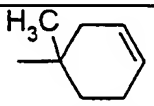
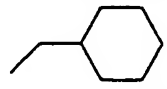
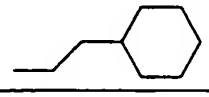
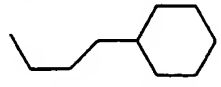
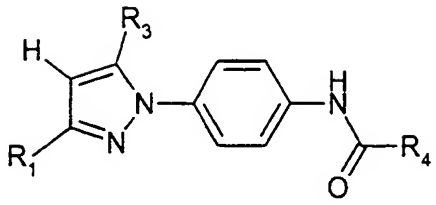
Cpd. #	R_1	R_3	R_4	m.p. °C
894	CF_3	Me		
896	CF_3	Me		
897	CF_3	Me	3-Quinolinyl	
899	CF_3	Me	(1-Et-3-Me)Pyrazol-5-yl	
902	CF_3	Me	(1-Me)Pyrrol-2-yl	
903	CF_3	Me		
909	CF_3	Me		
910	CF_3	Me	Cyclohexen-1-yl	
911	CF_3	Me		
912	CF_3	Me		
913	CF_3	Me	(1-Me)cyclohexyl	
914	CF_3	Me		
915	CF_3	Me		
915	CF_3	Me		

TABLE 1



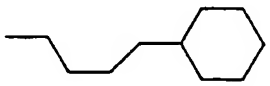
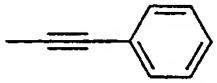
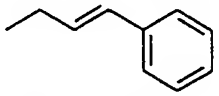
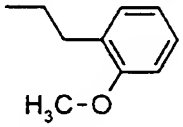
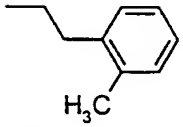
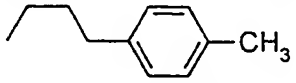
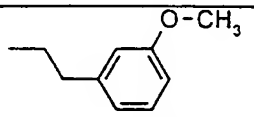
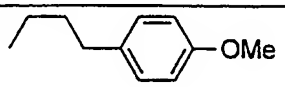
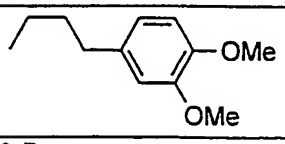
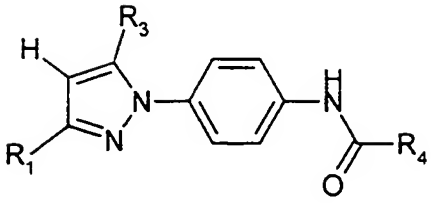
Cpd. #	R_1	R_3	R_4	m.p. °C
917	CF_3	Me		
918	CF_3	Me		
919	CF_3	Me		
920	CF_3	Me		
921	CF_3	Me		
922	CF_3	Me		
923	CF_3	Me		
924	CF_3	Me		
925	CF_3	Me		
927	2-Furyl	2-Furyl	3-Py	oil
928	*i*-Pr	3-Py	4-Py	oil
931	CF_3	Me	CH(Me)Et	
932	CF_3	Me	$CH_2CH=CHEt$	
933	CF_3	Me	$CH(Me)CH_2CH=CH_2$	
934	CF_3	Me	CH(Et)Et	

TABLE 1



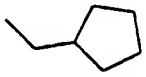
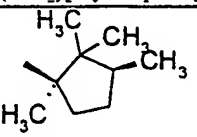
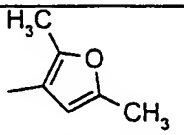
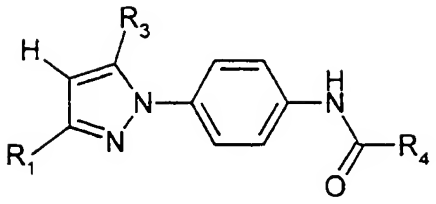
Cpd. #	R_1	R_3	R_4	m.p. °C
935	CF_3	Me	$CH2C(Me)_3$	
936	CF_3	Me	$(CH_2)_2CH(Me)Me$	
937	CF_3	Me	$CH_2CH_2NO_2$	
938	CF_3	Me	$C(Me)_2CH_2CH=CH_2$	
939	CF_3	Me	$C(Me)_2(CH_2)_2Me$	
940	CF_3	Me	(1-Methyl)cyclopropyl	
941	CF_3	Me	2-(Methyl)cyclopropyl	
942	CF_3	Me	(2,2,3,3-tetramethyl)cyclopropyl	
943	CF_3	Me	Cyclobutyl	
944	CF_3	Me		
945	CF_3	Me	Cycloheptyl	
946	CF_3	Me		
947	CF_3	Me	Cyclopenten-1-yl	
949	CF_3	Me		
950	CF_3	Me	$(CH_2)_2$Cyclopentyl	
951	CF_3	Me		
952	CF_3	Me		
954	CF_3	Me	(5-Me)-2-Thienyl	
955	Et	3-Py		

TABLE 1



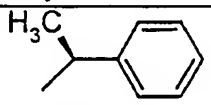
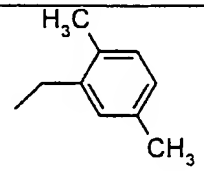
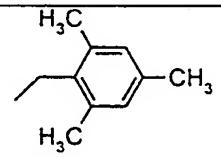
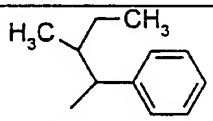
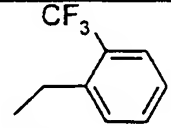
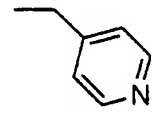
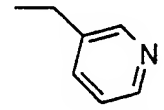
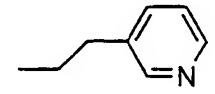
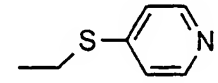
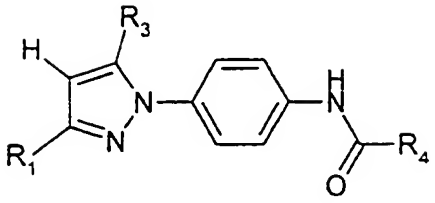
Cpd. #	R_1	R_3	R_4	m.p. °C
956	n-Heptyl	3-Py	3-Py	
958	CF_3	Me		
959	CF_3	Me		
962	CF_3	Me		
963	CF_3	Me		
964	CF_3	Me		
969	CF_3	Me		
970	CF_3	Me		
971	CF_3	Me		
972	CF_3	Me		
973	CF_3	Me	(4-vinyl)Ph	
974	CF_3	Me	(4-Acetyl)Ph	

TABLE 1



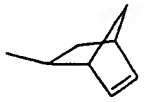
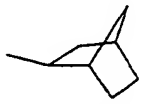
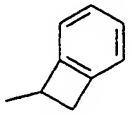
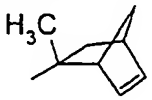
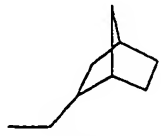
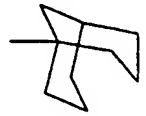
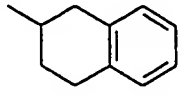
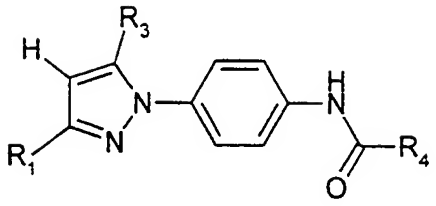
Cpd. #	R_1	R_3	R_4	m.p. °C
975	CF_3	Me	(4-*n*-Pr)Ph	
976	CF_3	Me	(4-CF_3O)Ph	
977	2-THF	Et	3-Py	119-121
978	CF_3	Me		
979	CF_3	Me		
980	CF_3	Me		
981	CF_3	Me		
982	CF_3	Me		
983	CF_3	Me		
984	CF_3	Me		
985	CF_3	Me		
988	CF_3	Me		

TABLE 1



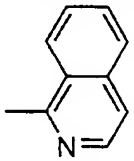
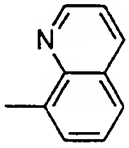
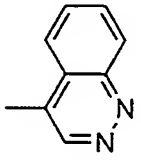
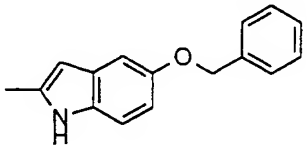
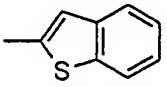
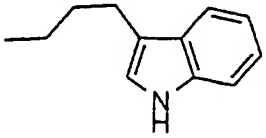
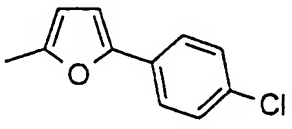
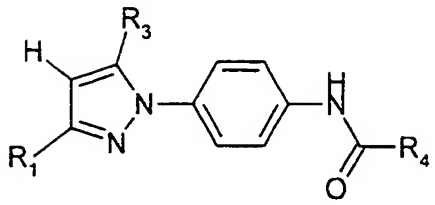
Cpd. #	R_1	R_3	R_4	m.p. °C
991	CF_3	Me	2-Quinolinyl	
992	CF_3	Me	4-Quinolinyl	
993	CF_3	Me		
994	CF_3	Me		
995	CF_3	Me		
996	CF_3	Me		
997	CF_3	Me		
998	CF_3	Me	(5-*n*-Bu)-3-Py	
999	CF_3	Me	[2-(1-Pyrrolyl)]Ph	
1000	CF_3	Me		
1001	CF_3	Me		

TABLE 1



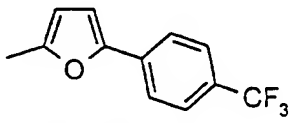
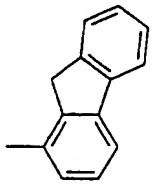
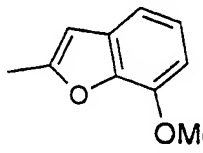
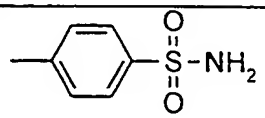
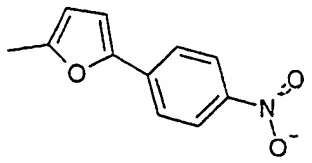
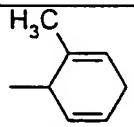
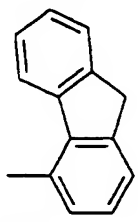
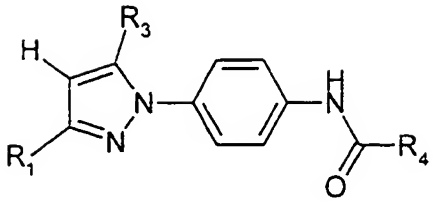
Cpd. #	R_1	R_3	R_4	m.p. °C
1002	CF_3	Me		
1003	CF_3	Me		
1004	CF_3	Me		
1005	CF_3	Me		
1006	CF_3	Me		
1008	CF_3	Me		
1010	CF_3	Me		
1011	*n*-Pr	CF_3	3-Py	122-123
1012	CF_3	*n*-Propyl	3-Py	178-179

TABLE 1



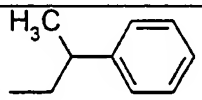
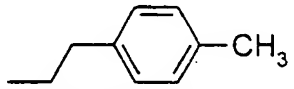
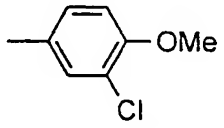
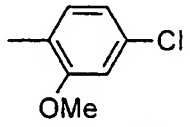
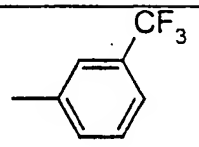
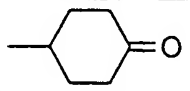
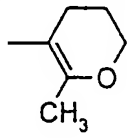
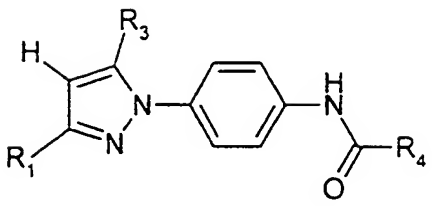
Cpd. #	R_1	R_3	R_4	m.p. °C
1013	CF_3	Me		
1014	CF_3	Me		
1015	CF_3	Me	(2-Ethoxy)Phenyl	
1017	CF_3	Me		
1018	CF_3	Me		
1019	CF_3	Me		
1021	[5-(3-Py)]-2-Furyl	CF_3	3-Py	218-219
1022	[5-(4-Py)]-2-Furyl	CF_3	3-Py	175-180
1023	[5-(5-Pyrimidinyl)]-2-Furyl	CF_3	3-Py	247-249
1024	3-Py	Et	(6-Cl)-3-Py	
1026	CF_3	Me		
1027	CF_3	Me		

TABLE 1



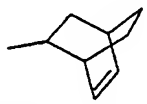
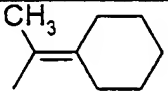
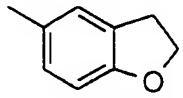
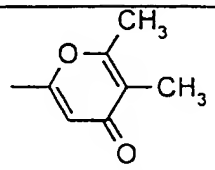
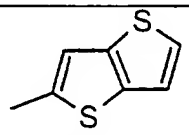
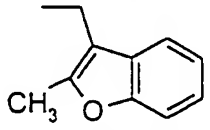
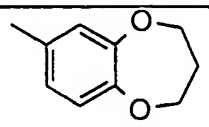
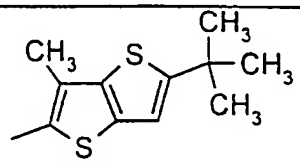
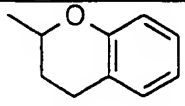
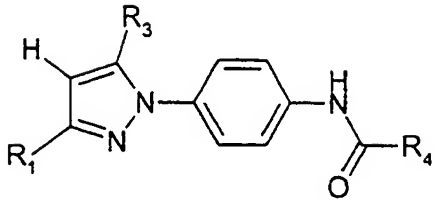
Cpd. #	R_1	R_3	R_4	m.p. °C
1028	CF_3	Me		
1029	CF_3	Me		
1030	CF_3	Me		
1031	CF_3	Me		
1032	CF_3	Me		
1033	CF_3	Me		
1034	CF_3	Me		
1035	CF_3	Me		
1036	CF_3	Me		

TABLE 1



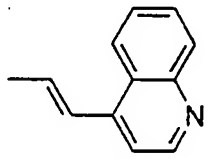
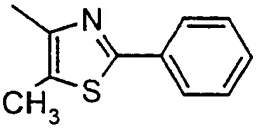
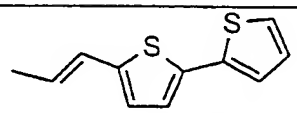
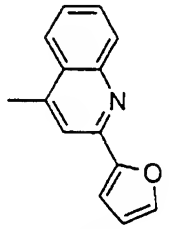
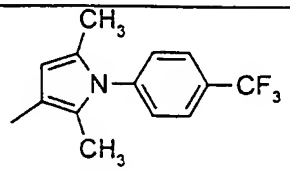
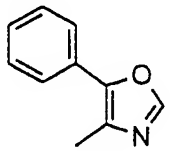
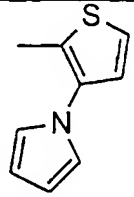
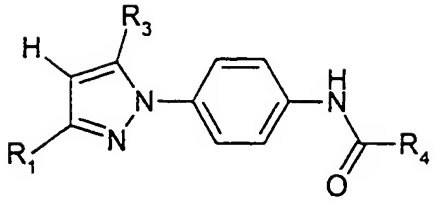
Cpd. #	R_1	R_3	R_4	m.p. °C
1037	CF_3	Me		
1040	CF_3	Me		
1041	CF_3	Me		
1042	CF_3	Me		
1043	CF_3	Me		
1047	CF_3	Me		
1048	CF_3	Me		

TABLE 1



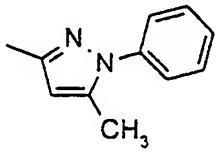
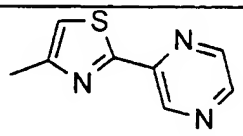
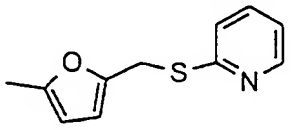
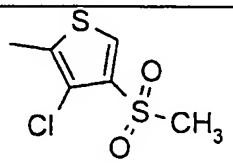
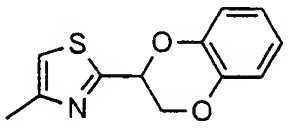
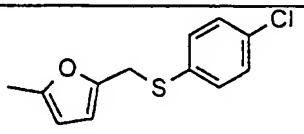
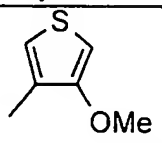
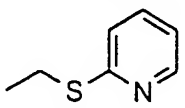
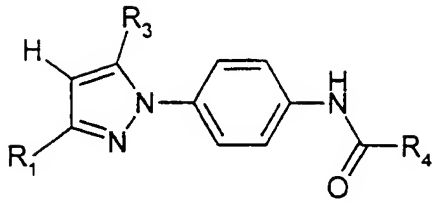
Cpd. #	R_1	R_3	R_4	m.p. °C
1050	CF_3	Me		
1051	CF_3	Me		
1052	CF_3	Me		
1053	CF_3	Me		
1054	CF_3	Me		
1055	CF_3	Me		
1056	(5-Br)-2-furyl	CF_3	3-Py	206-209
1057	2-Py	CF_3	3-Py	190-192
1058	CF_3	2-Py	3-Py	168-170
1061	CF_3	Me		
1062	CF_3	Me		

TABLE 1



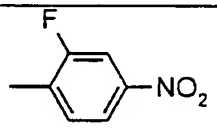
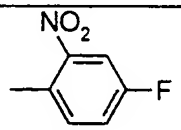
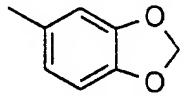
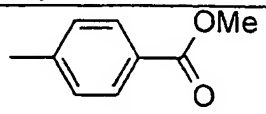
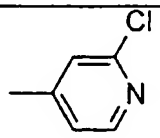
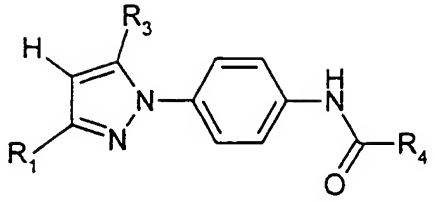
Cpd. #	R_1	R_3	R_4	m.p. °C
1065	CF_3	Me		
1066	CF_3	Me		
1069	(4-Fluoro)Ph	MeS	3-Py	208-210
1070	2-THF	CF_3	(4-Cyano)Phenyl	
1071	2-THF	CF_3		185-6
1072	4-Py	CF_3	3-Py	210-212
1075	CF_3	2-Furyl	3-Py	219-220
1076	2-THF	CF_3	(3,5-Dimethyl)-4-Isoxazolyl	132-134
1077	2-Furyl	MeS	(4-Chloro)Phenyl	176-178
1079	(2-OMe)-3-Py	Et	3-Py	
1080	(4-Cyano)Phenyl	*Et*		
1081	Et	*Et*		198-200
1083	3-Py	*i*-Pr	3-Py	90-92
1084	CF_3	(5-Bromo)-2-furanyl	3-Py	205-207
1087	CF_3	(5-(5-pyrimidinyl)-2-furanyl	3-Py	239-243
1088	MeS	2-Furyl	4-ClPh	186-188

TABLE 1



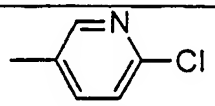
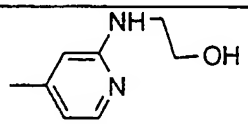
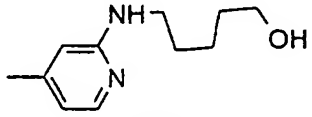
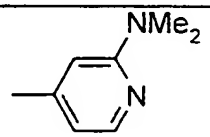
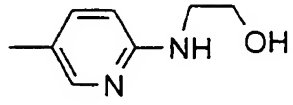
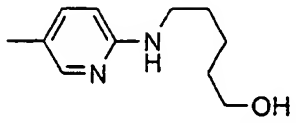
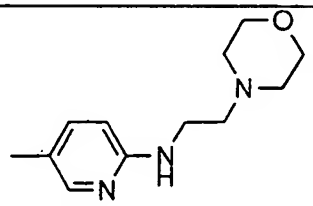
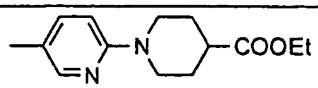
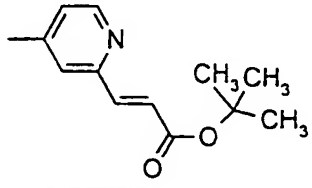
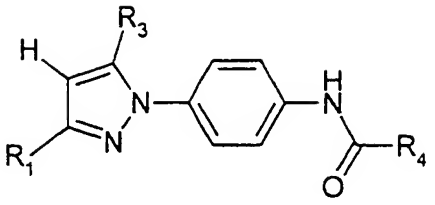
Cpd. #	R_1	R_3	R_4	m.p. °C
1089	Et	Et		170-172
1090	3-Py	CF_3		113-115
1091	3-Py	CF_3		93-95
1092	3-Py	CF_3		183-185
1093	3-Py	Et		95-97
1094	3-Py	Et		68-70
1095	3-Py	Et		72-75
1096	3-Py	Et		
1097	3-Py	Et		85-87

TABLE 1



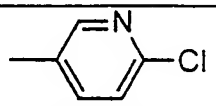
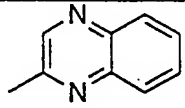
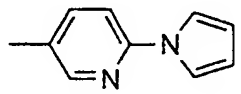
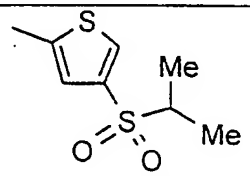
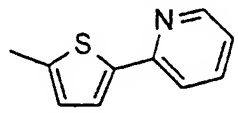
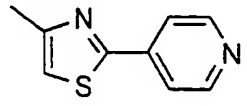
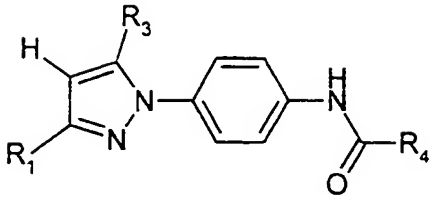
Cpd. #	R_1	R_3	R_4	m.p. °C
1100	2-THF	CF_3		
1101	2-furanyl	S(O)Me	(4-Chloro)Phenyl	110-110
1102	(5-Bromo)-3-Py	Et	3-Py	220-222
1103	2-THF	CF_3	(5-Nitro)-n-Pentyl	98-100
1106	MeO	Et	3-Py	
1107	CF_3	Me		
1108	CF_3	Me		
1109	CF_3	Me		
1110	CF_3	Me		
1111	CF_3	Me	(5-Methylsulfonyl)-2-thienyl	
1112	CF_3	Me		

TABLE 1



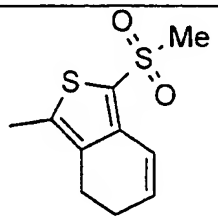
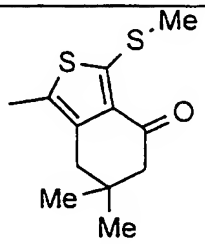
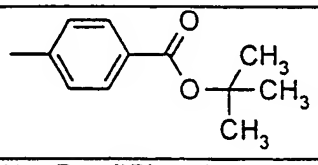
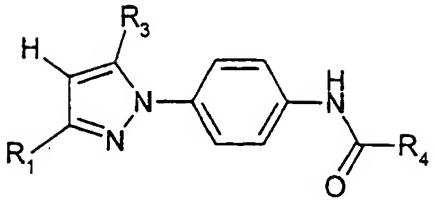
Cpd. #	R_1	R_3	R_4	m.p. °C
1113	CF_3	Me		
1114	CF_3	Me		
1115	CF_3	Me		
1117	CF_3	Me	(4-*n*-Butyl)Phenyl	
1118	CF_3	Me	(3-Methoxycarbonyl)Phenyl	
1119	CF_3	Me	(4-*n*-Propyloxy)Phenyl	

TABLE 1



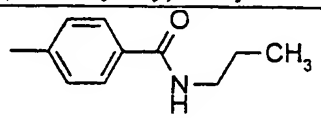
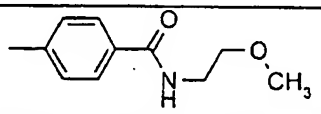
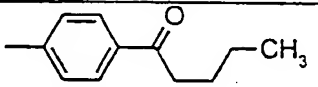
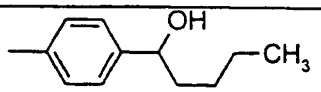
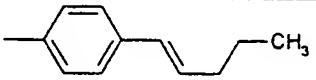
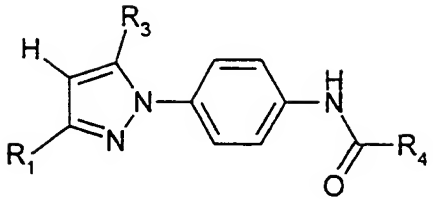
Cpd. #	R_1	R_3	R_4	m.p. °C
1120	CF_3	Me	(4-*n*-Butyloxy)Phenyl	
1121	CF_3	Me		
1122	CF_3	Me		
1123	CF_3	Me	(4-Ethoxycarbonyl)Phenyl	
1126	2-Py	CN	3-Py	237-239
1128	Dimethylamin omethyl	CF3	(4-Chloro)Phenyl	177-178
1130	(2-Chloro)-3-Pyridinyl	Et	3-Py	203-205
1131	(6-Chloro)-3-Pyridinyl	Et	3-Py	228-230
1134	2-THF	CF3	(2,4-Dinitro)Phenyl	180-182
1138	CF_3	Me		
1139	CF_3	Me		
1140	CF_3	Me		
1142	3-Py	SMe	3-Py	183-185
1149	CF_3	CH_3	(N-Methyl)-2-indolyl	
1150	CF_3	CH_3	(2-Nitro-4-chloro)phenyl	
1151	CF_3	CH_3	(2-phenethyl)phenyl	
1152	CF_3	CH_3	R-N-Methyl-2-pyrrolidinyl	
1162	3-py	Et	$CH=CH_2$	
1163	NMe_2	c-Pr	3-Py	
1165	MeS(O)	2-Furanyl	(4-Chloro)phenyl	
1167	i-Pr	Et	(6-Chloro)-3-Py	166-168
1169	4-Py	Et	3-Py	249-251

TABLE 1



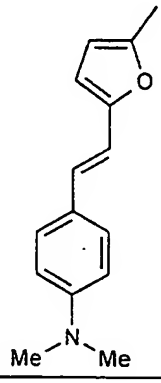
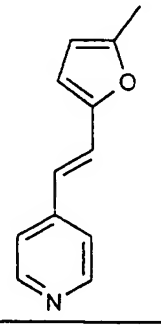
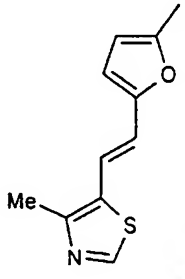
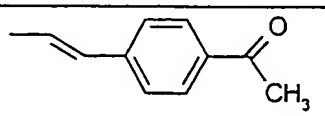
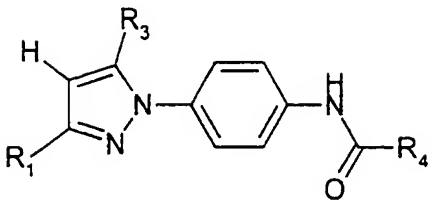
Cpd. #	R_1	R_3	R_4	m.p. °C
1170		CF_3	3-Py	232
1171		CF_3	3-Py	210-212
1172		CF_3	3-Py	193-6
1173	3-Py	Et		245-7
1174	2-furanyl	NMe_2	3-Py	
1175	NMe_2	2-furanyl	3-Py	

TABLE 1



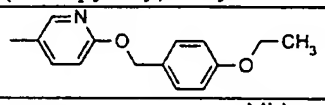
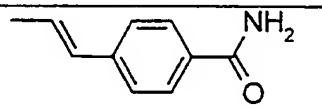
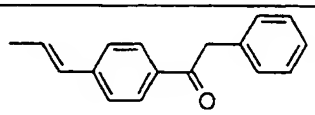
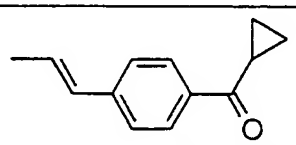
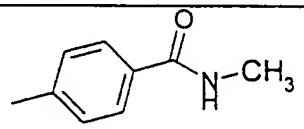
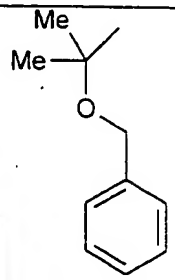
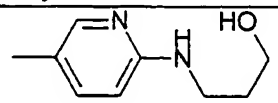
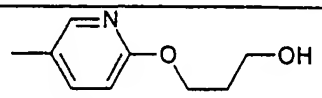
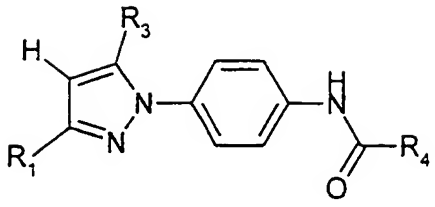
Cpd. #	R_1	R_3	R_4	m.p. °C
1177	i-Pr	$CH=CH_2$	3-Py	132-134
1178	c-Pr	CF_3	3-Py	185-186
1179	3-Py	Et	(6-Propyloxy)-3-Py	70-72
1180	3-Py	Et		200-202
1183	3-Py	Et		263-266
1184	3-Py	Et		196-199
1185	3-Py	Et		215-218
1189	CF_3	Me		273-274
1192		Et	3-Py	123-125
1193	CF_3	c-Pr	3-Py	181-183
1194	3-py	Et		180-182
1195	3-py	Et		153-155

TABLE 1



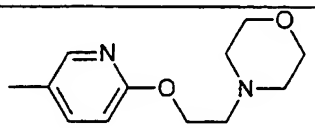
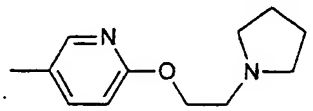
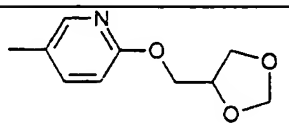
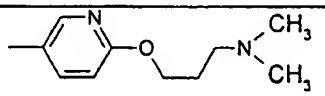
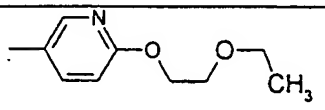
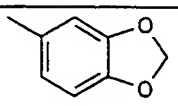
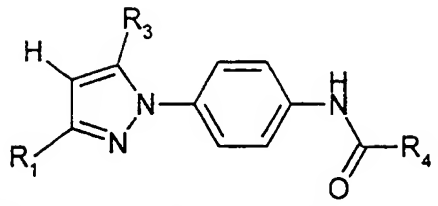
Cpd. #	R_1	R_3	R_4	m.p. °C
1196	3-py	Et		
1197	3-py	Et		
1199	i-Pr	Et	(2-methyl)-3-dihydropyranyl	133-134
1200	i-Pr	Et	(3,5-dimethyl)-4-isoxazolyl	173-175
1207	CF_3	Et	(1,4-dimethyl)-5-imidazolyl	179-182
1211	3-py	Et		
1212	3-Py	Et		
1213	3-Py	Et		
1215	i-Pr	Et		214-216

TABLE 1



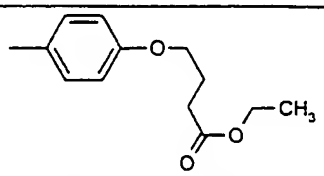
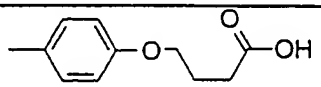
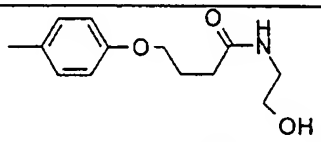
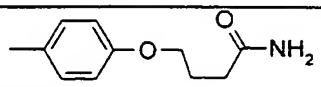
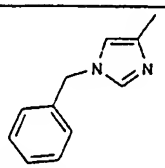
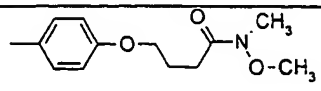
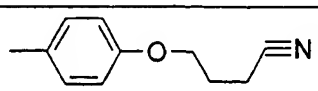
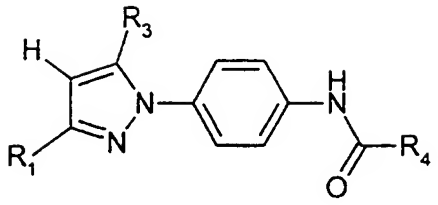
Cpd. #	R_1	R_3	R_4	m.p. °C
1240	CF_3	Et		169-170
1241	CF_3	Et		183-185
1242	CF_3	Et		236-238
1243	CF_3	Et		208-209
1244		Me	3-Py	
1245	CF_3	CH_2CN	3-Py	168-169
1249	N-pyrrolidinyl	Et	3-Py	188-191
1265	CF_3	Et		
1266	CF_3	Et		151-153

TABLE 1



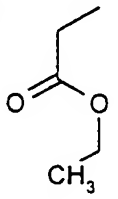
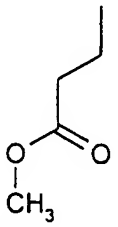
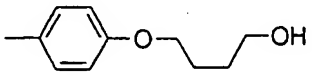
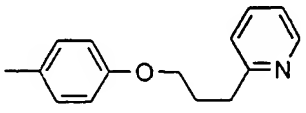
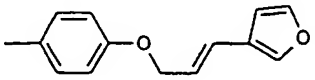
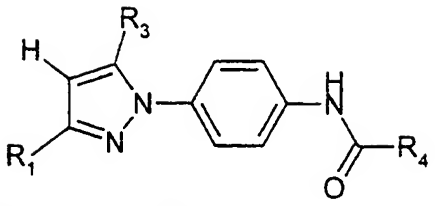
Cpd. #	R_1	R_3	R_4	m.p. °C
1267		$CH=CH_2$	3-Py	
1272	i-Pr	Et	4-Py	
1275		$CH=CH_2$	3-Py	
1277	EtO-	Et	3-Py	127-130
1278	EtO(C=O)-	Et	3-Py	168-170
1279	CF_3	Et		179-180
1280	CF_3	Et		181-182
1284	CF_3	Et		193-194

TABLE 1



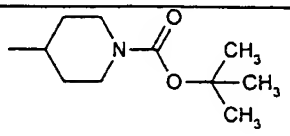
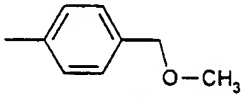
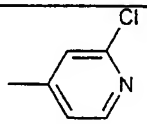
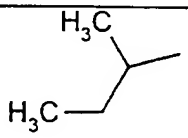
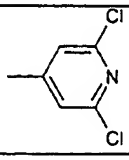
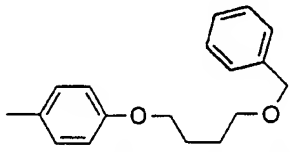
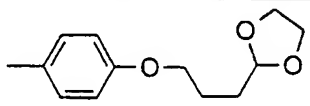
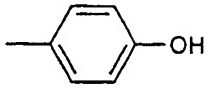
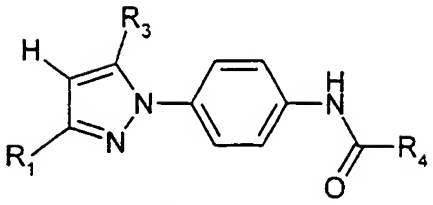
Cpd. #	R_1	R_3	R_4	m.p. °C
1285	i-Pr	Et		
1286	i-Pr	Et		144-146
1304	i-Pr	Et		213-215
1306		Et	3-Py	
1307	i-Pr	Et		88-91
1308	CF_3	Et		92-93
1309	CF_3	Et		158-159
1310	CF_3	Et		282-283

TABLE 1



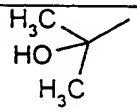
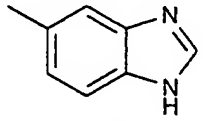
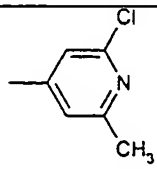
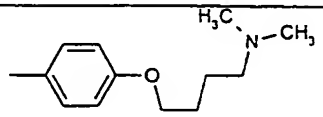
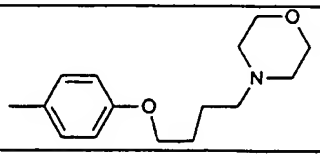
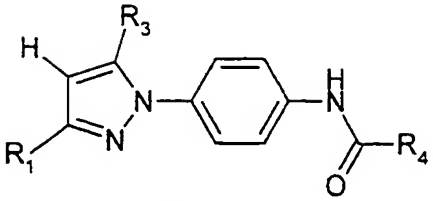
Cpd. #	R_1	R_3	R_4	m.p. °C
1311	3-Py	Et	2-Pyrazinyl	191-192
1312	i-Pr	Et	2-Pyrazinyl	169-171
1313		Et	3-Py	81-83
1316	i-Pr	Et		128-130
1317	i-Pr	Et		
1320	CF_3	Et		
1321	CF_3	Et		

TABLE 1



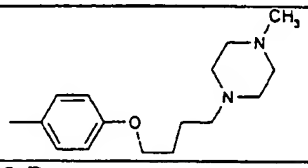
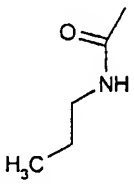
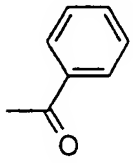
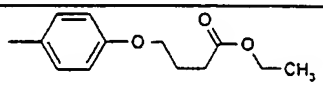
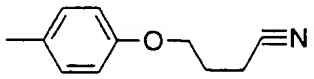
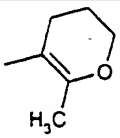
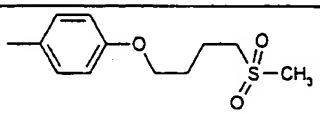
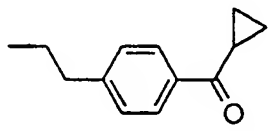
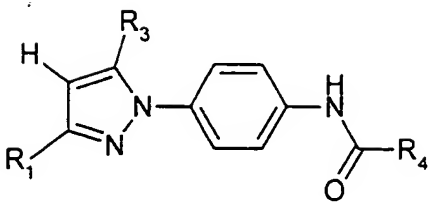
Cpd. #	R_1	R_3	R_4	m.p. °C
1322	CF_3	Et		
1323		Et	3-Py	
1330	CF_3	Et		125-126
1334	3-Py	Et		161-163
1335	3-Py	Et		144-145
1336	3-Py	Et		157-158
1338	CF3	Et		169-171
1339	c-Pentyl	CF3	3-Py	143-145
1340	i-Pr	Et		130-134

TABLE 1



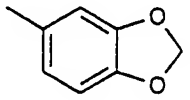
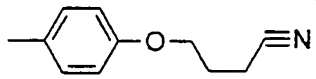
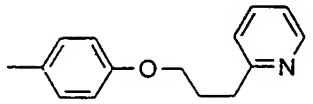
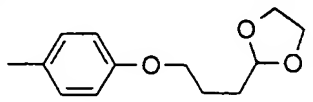
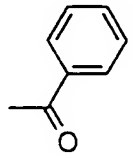
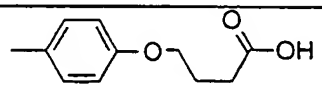
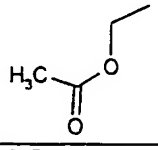
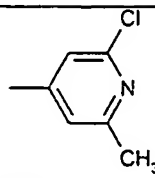
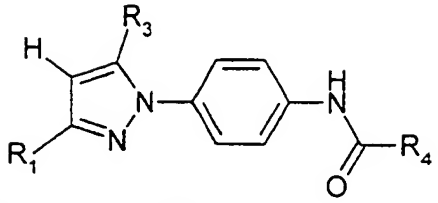
Cpd. #	R_1	R_3	R_4	m.p. °C
1345	3-Py	Et		
1346	i-Pr	Et		
1347	3-Py	Et		143-144
1348	3-Py	Et		136-137
1349	3-Py	Et		136-137
1350	3-Py	Et		219-221
1352		Et	Py	105-106
1360	3-Py	Et		
1362	i-Pr	CN	3-Py	

TABLE 1



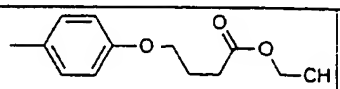
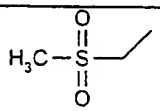
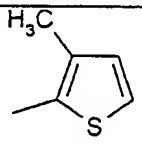
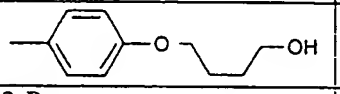
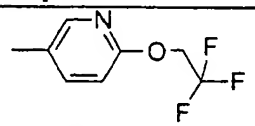
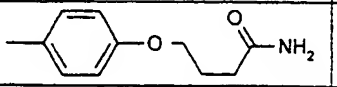
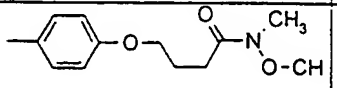
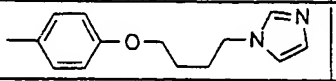
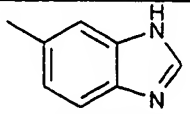
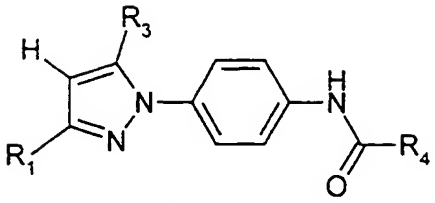
Cpd. #	R_1	R_3	R_4	m.p. °C
1363	i-Pr	Et		
1368		Et	3-Py	
1370	3-Py	Et	2-thienyl	
1371	3-Py	Et	3-thienyl	
1372	3-Py	Et		
1374	2-naphthyl	CF3	3-Py	225
1375	CF3	2-naphthyl	3-Py	203
1378	3-Py	Et		
1380	$-CH_2CN$	Et	3-Py	
1381	3-Py	Et		
1383	3-Py	Et		
1384	3-Py	Et		161-163
1385	CF_3	Et		201-203
1394	3-Py	Et		
1395	3-Py	Et	(2-Methyl)-3-Py	

TABLE 1



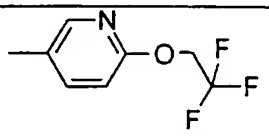
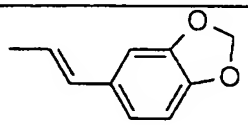
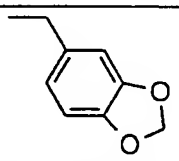
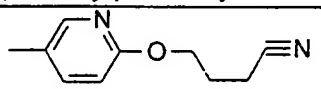
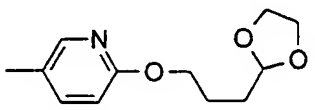
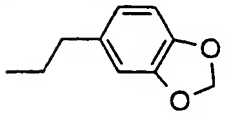
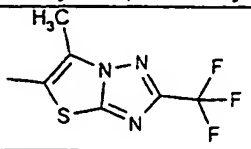
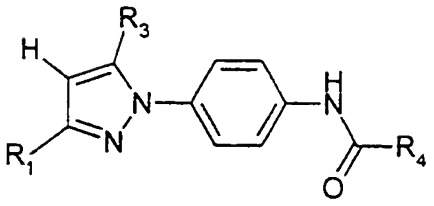
Cpd. #	R_1	R_3	R_4	m.p. °C
1397	i-Pr	Et		
1403	3-Py	Et		
1404	3-Py	Et		
1408	3-py	Et	(3,5-dimethyl)-5-isoxazolyl	
1412	3-py	Et	(2-chloro)-3-py	
1414	3-py	Et	(2-methyl)-3-furanyl	
1422	3-py	Et		
1423	3-py	Et		150-152
1426	3-py	Et	(2-ethyl)phenyl	
1428	3-Py	Et		157-159
1429	3-py	CN	3-Py	230-232
1432	3-Py	Et	(5-Methyl)-4-isoxazolyl	
1448	CN	3-Py	3-Py	211-212
1451	3-py	Et	(3-methyl-4-vinyl-5-methylthio)-2-thienyl	
1465	3-Py	Et		

TABLE 1



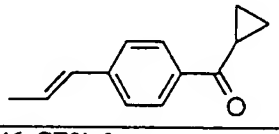
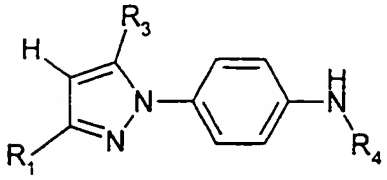
Cpd. #	R_1	R_3	R_4	m.p. °C
1467	3-py	Et	(1-methyl)cyclohexyl	89-90
1468	3-py	Et	(2-methyl)cyclohexyl	91-92
1469	3-py	Et	cyclohexyl	152-153
1473	3-py	Et	Cyclopentyl	134-135
1484	3-py	Et	(2-methyl)phenyl	179-180
1494	i-Pr	Et		210-214
1502	3-py	Et	(6-CF3)-3-py	
1506	3-py	Et	(4-CF3)-3-py	
1511	3-py	$CH=CH_2$	3-py	

TABLE 2

Compounds with L is -NH-



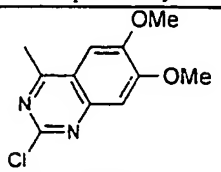
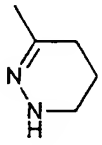
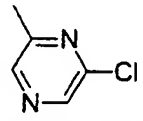
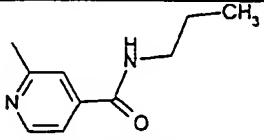
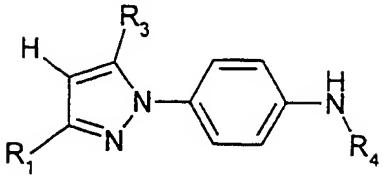
Cpd. #	R_1	R_3	R_4	m.p. °C
580	CF_3	CF_3	(7-Trifluoromethyl)-4-quinolyl	230
615	CF_3	CF_3	2-Py	117-119
616	CF_3	CF_3	(3-NO_2)-2-Py	118-120
644	CF_3	CF_3	2-benzimidazolyl	220-222
648	CF_3	CF_3	1-isoquinolinyl	205-220
654	CF_3	CF_3		240-242
655	CF_3	CF_3	(3-Cl)-2-Py	92-93
656	CF_3	CF_3	(3-CN)-2-Py	133-135
657	CF_3	CF_3	2-Quinolyl	
679	CF_3	CF_3	(3-Chloro-5-trifluoromethyl)-2-pyridyl	104-105
683	CF_3	Cl	1-isoquinolinyl	244-254
694	CF_3	CF_3		
699	CF_3	CF_3		167-168
702	CF_3	CF_3	(6-Cl)-Pyrimidin-4-yl	149-150
718	CF_3	CF_3	2-Pyrazinyl	
720	CF_3	CF_3		
732	1-Furyl	CF_3	1-isoquinolinyl	191-193
783	3-Py	CF_3	1-isoquinolinyl	204-205
1158	3-Py	Et	1-isoquinolinyl	136-138

TABLE 2

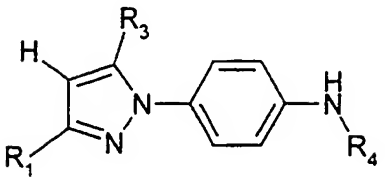
Compounds with L is -NH-



Cpd. #	R_1	R_3	R_4	m.p. °C
1159	i-Pr	Et	1-isoquinolinyl	
1160	i-Pr	Et	(3-cyano)-2-pyridyl	123-124
1333	i-Pr	Et	cyclohexyl	
1398	3-Py	Et	phenyl	
1430	3-Py	Et	3-pyridyl	
1436	3-Py	Et	R-1-indanyl	
1437	3-Py	Et	S-1-indanyl	
1438	3-Py	Et	3-phenylphenyl	
1439	3-Py	Et	2-phenylphenyl	
1440	3-Py	Et	3-methylphenyl	
1441	3-Py	Et	2-methylphenyl	
1442	3-Py	Et	3-methoxyphenyl	
1443	3-Py	Et	2-methoxyphenyl	
1444	3-Py	Et	1-naphthyl	
1449	3-Py	Et	4-[4,5,6,7-tetrahydrobenzothiopenyl]	145-146
1456	3-Py	Et	4-methyl-7-bromo-1-indanyl	
1457	3-Py	Et	8-bromo-1-indanyl	68-72
1464	3-Py	Et	2-nitrophenyl	135-137
1466	3-Py	Et	2-cyanophenyl	148-150
1476	3-Py	Et	Cyclohexyl	
1478	3-Py	Et	S-1-(1,2,3,4-tetrahydronaphthyl)	147-149
1479	3-Py	Et	R-1-(1,2,3,4-tetrahydronaphthyl)	150-152
1485	3-Py	Et	2-methoxy-6-methylphenyl	
1486	3-Py	Et	2-chloro-6-methylphenyl	
1492	3-Py	Et	4-tetrahydropyranyl	
1493	3-Py	Et	4-ethoxycarbonylcyclohexyl	
1495	2-tetrahydrofuranyl	CF_3	1-isoquinolinyl	
1501	3-Py	Et	2-methylcyclohexyl	

TABLE 2

Compounds with L is -NH-



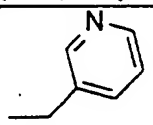
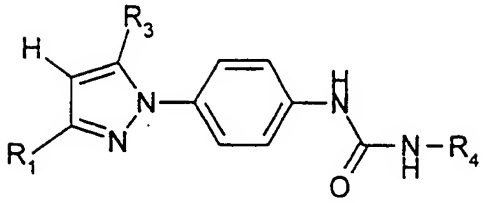
Cpd. #	R_1	R_3	R_4	m.p. °C
585	CF_3	CF_3	4-ClPh	263-264
862	CF_3	CF_3	(6-Cl)-3-Py	244-245
863	CF_3	CF_3		143-146
864	CF_3	CF_3	(4-Cyano)Phenyl	247
886	CF_3	CF_3	4-Pyrimidinyl	218-219
887	CF_3	CF_3	3-Py	152-155

TABLE 3

Compounds with L is –NHC(O)NH--



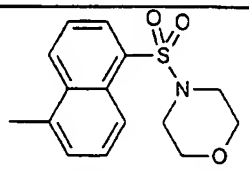
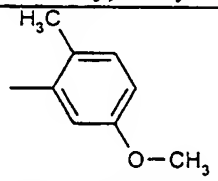
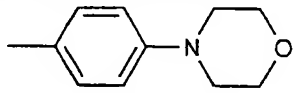
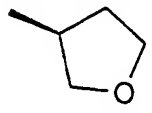
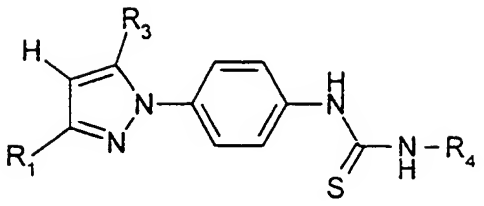
Cpd. #	R_1	R_3	R_4	m.p. °C
908	CF_3	CF_3		220-222
1387	3-Py	Et	Cyclohexyl	197
1391	3-Py	Et	(2-Methyl-4-Methoxy)Phenyl	228
1400	3-Py	Et		
1401	3-Py	Et	4-bromophenyl	
1402	3-Py	Et	3-Py	
1405	3-Py	Et	(4-Butoxy)Phenyl	192
1406	3-Py	Et		227
1409	3-Py	Et		153-155

TABLE 4

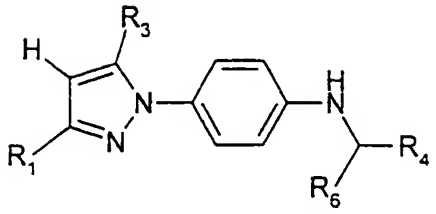
L is –NHC(S)NH--



Cpd. #	R_1	R_3	R_4	m.p. °C
1098	2-Furanyl	CF_3	4-ClPh	
1099	2-Furanyl	CF_3	3-Py	

TABLE 5

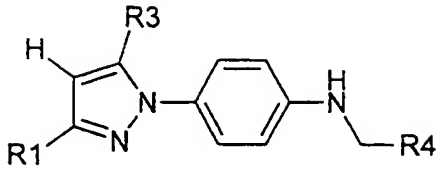
L is –NHCH(R_5)-



Cpd. #	R_1	R_3	R_4	R_5	m.p. °C
740	CF_3	CF_3	Ph	*n*-Bu	
753	CF_3	CF_3	Ph	CN	119-121
754	CF_3	CF_3	Ph	(2-F)-3-Py	
1078	CF_3	CF_3	Ph	$-CH_2-SO-CH_3$	
1328	i-Pr	Et	Ph	$-CH_2OH$	
1342	i-Pr	Et	Ph	$-CH_2CH_2OH$	
1373	3-Py	Et	3-Py	CN	
1474	3-Py	Et	Ph	Me	
1480	3-Py	Et	Cyclohexyl	Me	
1515	3-Py	Et	Cyclopentyl	Me	

TABLE 6

L is $-NHCH_2$



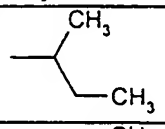
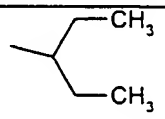
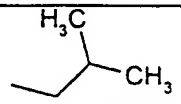
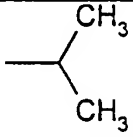
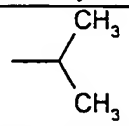
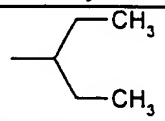
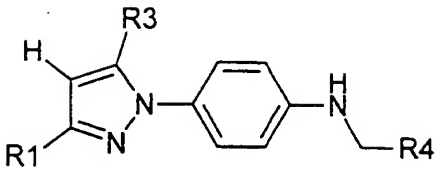
CMPD #	R_1	R_3	R_4	m.p. °C
548	CF_3	CF_3	(4-Chloro)phenyl	89-90
592	CF_3	Me	(4-Chloro)phenyl	
613	CF_3	CF_3	Me	54
769	2-Furanyl	CF_3	3-Py	105-106
842	2-THF	CF_3	3-Py	
1154	CF_3	Me		
1155	CF_3	Me		
1156	CF_3	Me		
1157	CF_3	Me		
1166	3-Py	Et	n-Pentyl	
1186	3-Py	Et		
1187	3-Py	Et	(4-Propyloxy)Phenyl	
1188	3-Py	Et	(4-Trifluoromethoxy)Phenyl	
1191	3-Py	Et	3-furanyl	
1198	i-Pr	Et		
1201	i-Pr	Et	(3,5-Dimethyl)-4-isoxazolyl	87-88
1203	3-Py	Et	Phenyl	
1204	3-Py	Et	(4-Methoxy)Phenyl	
1205	3-Py	Et	(4-Bromo)Phenyl	
1206	i-Pr	Et	3-Py	
1216	3-Py	Et	(2-Chloro)Phenyl	

TABLE 6

L is $-NHCH_2$



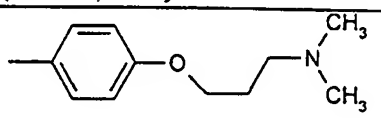
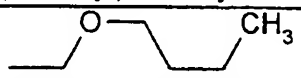
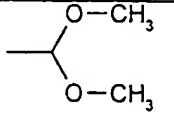
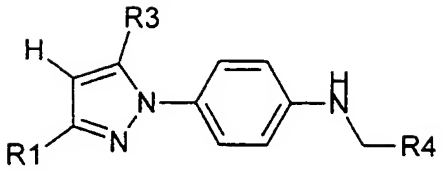
CMPD #	R_1	R_3	R_4	m.p. °C
1218	3-Py	Et	(2-Nitro)Phenyl	
1219	3-Py	Et		
1222	3-Py	Et	(2,6-Dimethoxy)Phenyl	
1223	3-Py	Et	(2-Chloro-6-Nitro)Phenyl	
1224	3-Py	Et	(2,5-Dimethyl)Phenyl	
1226	3-Py	Et	(3-Methyl)Phenyl	
1227	3-Py	Et	(3,5-Dimethoxy)Phenyl	
1228	3-Py	Et	(3-Nitro)Phenyl	
1229	3-Py	Et	(3,4-Dimethoxy)Phenyl	
1230	3-Py	Et	(3-Benzyloxy)Phenyl	
1231	3-Py	Et	(2,3-Dimethoxy)Phenyl	
1233	3-Py	Et	(3-Trifluoromethoxy)Phenyl	
1235	3-Py	Et	(3-Cyano)Phenyl	
1236	3-Py	Et	(3,4-methylenedioxy)Phenyl	
1237	3-Py	Et	(4-Methylthio)Phenyl	
1238	3-Py	Et	(4-Ethoxy)Phenyl	
1246	CF_3	Et	(4-Methoxycarbonyl)Phenyl	93-95
1247	CF_3	Et	(3-Methyl)-2-thienyl	93-95
1248	CF_3	Et	(5-Methyl)-2-thienyl	87-89
1250	3-Py	Et		
1252	3-Py	Et	(4-Trifluoromethyl)phenyl	
1253	3-Py	Et	(2,5-Dimethoxy)Phenyl	
1254	3-Py	Et	(4-Propyloxy)Phenyl	
1255	3-Py	Et	cyclohexyl	
1256	3-Py	Et	(2-Methoxy)Phenyl	
1257	3-Py	Et		

TABLE 6

L is $-NHCH_2$



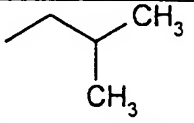
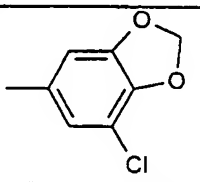
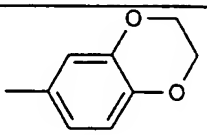
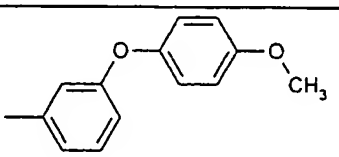
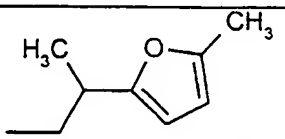
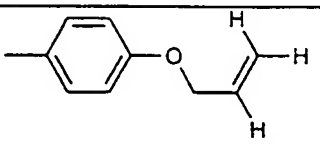
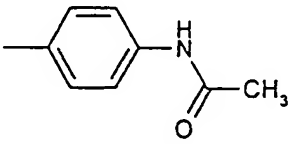
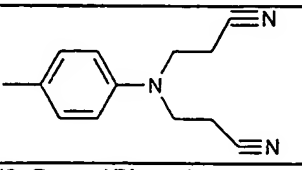
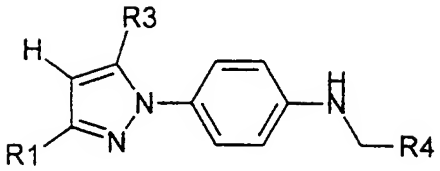
CMPD #	R_1	R_3	R_4	m.p. °C
1258	3-Py	Et		
1259	3-Py	Et		
1260	3-Py	Et		
1261	3-Py	Et		
1262	3-Py	Et		
1263	3-Py	Et		
1282	3-Py	Et		
1283	3-Py	Et		
1287	3-Py	Et	(2-Cyano)Phenyl	

TABLE 6

L is $-NHCH_2$



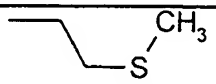
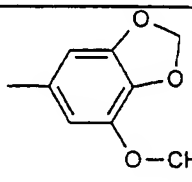
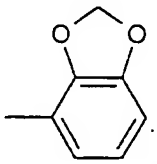
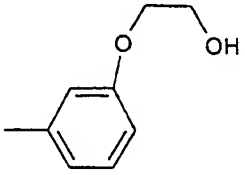
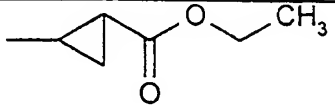
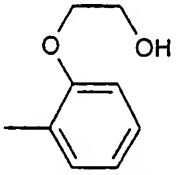
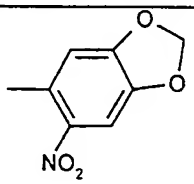
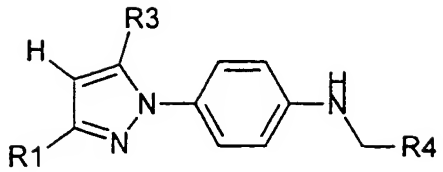
CMPD #	R_1	R_3	R_4	m.p. °C
1288	3-Py	Et		
1289	3-Py	Et		
1290	3-Py	Et		
1291	3-Py	Et		
1292	3-Py	Et		
1294	3-Py	Et		
1295	3-Py	Et		

TABLE 6

L is $-NHCH_2$



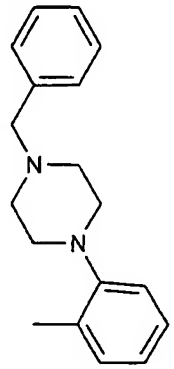
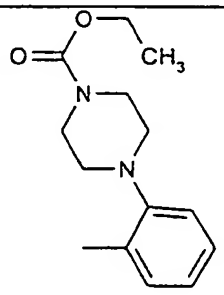
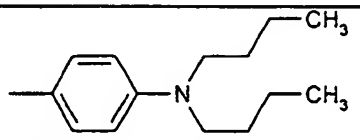
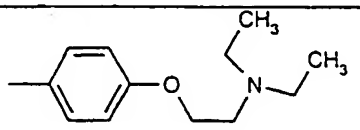
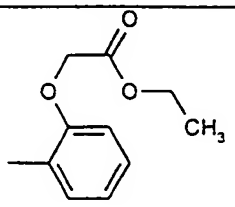
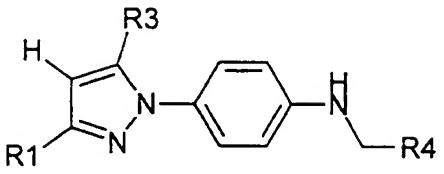
CMPD #	R_1	R_3	R_4	m.p. °C
1296	3-Py	Et		
1297	3-Py	Et		
1298	3-Py	Et		
1299	3-Py	Et		
1300	3-Py	Et		

TABLE 6

L is $-NHCH_2$



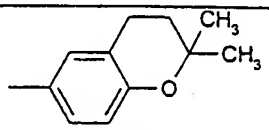
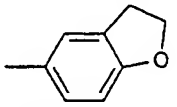
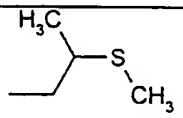
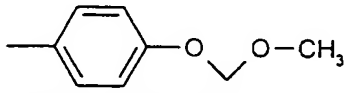
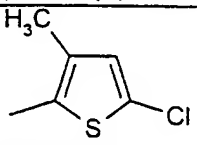
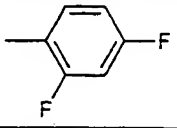
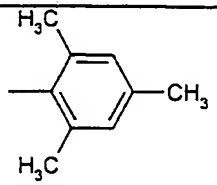
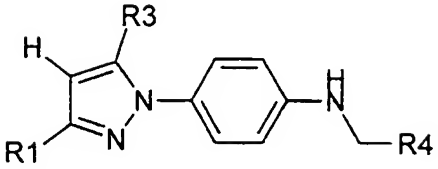
CMPD #	R_1	R_3	R_4	m.p. °C
1301	3-Py	Et		
1302	3-Py	Et		
1303	3-Py	Et		
1314	3-Py	Et		
1337	3-Py	Et	(3-Methyl)-2-thienyl	
1376	i-Pr	Et	(3-Methyl)-2-thienyl	
1382	3-Py	Et		
1389	3-Py	Et	2-thienyl	
1396	3-Py	Et	(2-Methyl)-3-pyridinyl	
1410	3-Py	Et		100-101
1411	3-Py	Et		180-181
1413	3-Py	Et	(2-Chloro)-3-Pyridinyl	

TABLE 6

L is $-NHCH_2$



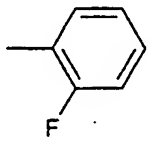
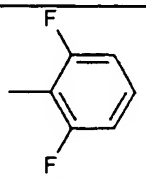
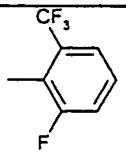
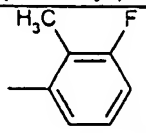
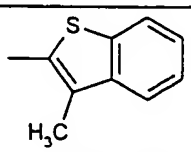
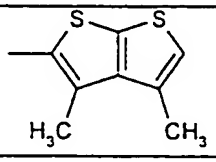
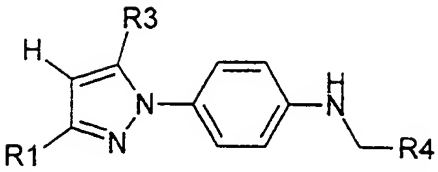
CMPD #	R_1	R_3	R_4	m.p. °C
1417	3-Py	Et		
1418	3-Py	Et		
1419	3-Py	Et	(2-Trifluoromethyl)Phenyl	
1420	3-Py	Et		
1421	3-Py	Et	(3,5-dimethyl)-4-isoxazolyl	
1424	3-Py	Et	(2-Methyl)-3-furanyl	
1425	3-Py	Et	(2-Ethyl)-Phenyl	
1431	3-Py	Et	(5-Methyl)-4-isoxazolyl	
1447	3-Py	CN	(3-Methyl)-2-thienyl	136-137
1458	3-Py	Et		101-103
1459	3-Py	Et		130
1460	3-Py	Et		179-182

TABLE 6

L is $-NHCH_2$



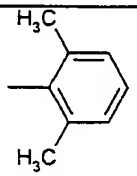
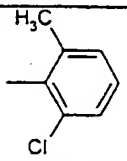
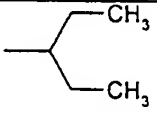
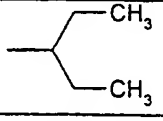
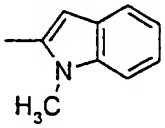
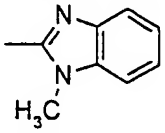
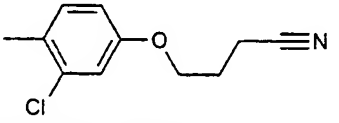
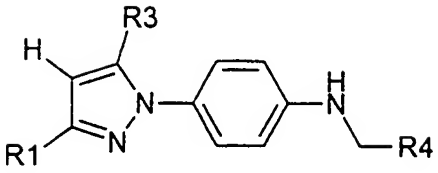
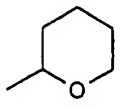
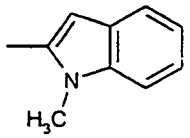
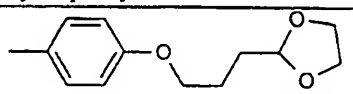
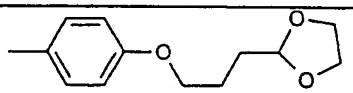
CMPD #	R_1	R_3	R_4	m.p. °C
1461	3-Py	Et		174-175
1462	3-Py	Et		152-153
1470	3-Py	Et	cyclopentyl	
1471	3-Py	Et	(2-Methyl)cyclohexyl	
1472	3-Py	Et	(1-Methyl)cyclohexyl	
1483	3-Py	Et	3-Py	
1487	3-Py	Et		66-67
1488	3-Py	CN		95-96
1490	3-Py	Et		161-163
1491	3-Py	Et		
1496	3-Py	Et	(3-Bromo)-2-thienyl	
1499	3-Py	Et	4-pyridinyl	
1505	3-Py	Et		
1507	3-Py	CN	(2-methyl)phenyl	

TABLE 6

L is –NHCH$_2$



CMPD #	R_1	R_3	R_4	m.p. °C
1514	3-Py	Et		
1518	3-Py	CN		181
1520	3-Py	CN	Cyclopentyl	131-133
1521	3-Py	Et		94-96
1522	3-Py	CN		122-124
1525	3-Py	Et	(3-Chloro)-2-thienyl	

Assessment of Biological Properties

IL-2 Promoter Assay

The IL-2 promoter assay measures transcriptional activation of a luciferase reporter gene which has been placed under control of the IL-2 promoter/enhancer. All the known regulatory features of the IL-2 gene are contained within a ~300 bp sequence immediately upstream of the open reading frame. The region -328 to +35 relative to the transcription start site of the IL-2 gene is obtained by RT-PCR of human genomic DNA and is subcloned into the promoterless luciferase reporter vector pGL2-Basic (Promega). The resulting construct, pIL2P-luc, and a vector containing a neomycin resistance gene, pcDNA/Neo (Invitrogen), are

linearized and stably transfected into Jurkat cells (a human T cell line) by electroporation. Following G-418 selection and dilution cloning, a cell line was established, J.1F/C6., which exhibited a strong induction of luciferase activity upon treatment with ionomycin and PMA (up to 100-fold), and potent inhibition by FK506 (IC_{50} = 0.3 nM).

For screening compounds, the cells are pelleted by centrifugation, washed once with PBS, resuspended in RPMI (phenol red-free) containing 5% FBS, and dispensed into 96-well, white microtiter plates (Packard) at 50,000 cells/well. The cells are pre-incubated with compounds (1 μg/ml) for 15 min prior to addition of ionomycin (1 μg/ml) and PMA (10 ng/ml) in a final volume of 100 μl. Following a 5 hr incubation at 37°C in a humidified incubator, 100 μl of Luc-Lite lysis buffer/luciferase assay buffer (Promega) is added and luminescence measured using a Packard TopCount scintillation counter/luminometer.

Representatives from the synthetic examples and theTables above were screened in this assay and had IC_{50}s below 10 microM

IL-2 Production Assay

Human peripheral blood is obtained from healthy donors by venipuncture and the mononuclear cell fraction is prepared by centrifugation on Ficoll Hypaque (Phamacia) density gradients. Contaminating red blood cells are lysed and the CD3+/CD4+ cells are purified using immunoaffinity columns (R&D Systems or CellPro). The cells are resuspended and dispensed in 96 well microtiter plates. Test compounds are added to the cells approximately 15 minutes prior to stimulation with ionomycin (1 μg/ml) and PMA (10 ng/ml). The final volume of the assay is 100 μL. Following a 16 hr incubation at 37°C, the cells are pelleted by centrifugation, and the supernatants are collected and stored at -70°C until assayed for IL-2 using a commercial ELISA kit (Genzyme).

Representatives from the synthetic examples and theTables above were screened in this assay and had IC_{50}s below 10 microM

Allogeneic Cell Transplant Response in Mice

The ability of cells to recognize other cells from self or from another genetically different individual (non-self) is an important property in maintaining the integrity of tissue and organ structure. The allogeneic cell transplant response is therefore an important model for studies of transplant rejection. This T-cell-mediated immune response can be induced in adult mice by the injection of lymphocytes from an histoincompatible mouse strain. This response is characterized by T cell proliferation which is limited to the popliteal lymph node that receives drainage from the footpad area. No in vitro system exists that can exactly duplicate completely this in vivo response. The assay is commonly used to evaluate new and novel potential immunosuppressive molecules. The assay is preferred to the local GVH response in mice because the magnitude of the response is significantly greater (Kroczek et al., J. Immunology, 139, 3597 (1987)).

Experiments are conducted using male or female mice (20-26 grams). Any histoincompatible mouse strains suffice for donor and recipient populations. Typically DBA mice are used as donors and C57Bl/6 mice are used as recipients. A minimum of 1 week stabilization and conditioning period is usually required before use of the mice. Each study utilizes approximately 36 recipient mice divided into groups of 6. Previous studies suggest this is the minimum number of animals which yields statistically significant results.

Donor mice are sacrificed by CO_2 asphyxiation and spleens are removed and a cell suspension is prepared. The cell suspension (1.0×10^7/metatarsal in 0.05 ml) is injected I.D. into the dorsal metatarsal skin of recipient mice. Four days later, the animals are sacrificed by CO_2 asphyxiation and the popliteal nodes are removed and weighed. Groups of mice receiving putative immunosuppressive agents are dosed subcutaneously, intraperitoneally or orally one hour prior to cell injection and daily thereafter. The tests last approximately four days. The assay involves no footpad swelling and only a moderate increase in the size of the popliteal lymph node. The Student's t test is used to determine significant differences between popliteal lymph nodes of groups of untreated mice and those mice treated with putative immunosuppressive agents.

Table 7

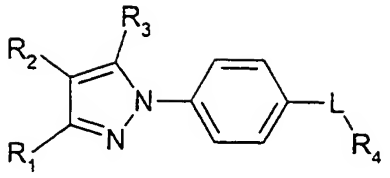
Results of Allogeneic Cell Transplant Model in Mice

Cpd. #	Dose (mg/kg p.o., b.i.d.)	% Inhibition
826 (Table 1)	100	74

While we have described a number of embodiments of this invention, it is apparent that our basic constructions may be altered to provide other embodiments which utilize the products and methods of this invention. Therefore, it will be appreciated that the scope of this invention is to be defined by the appended claims, rather than by the specific embodiments that have been presented herein by way of example.

WHAT IS CLAIMED IS:

1. A compound of formula I



wherein:

R_1 and R_3 are the same or different and each is CF_3, halogen, CN, C_{1-8} alkyl or branched alkyl or C_{1-8} alkenyl or branched alkenyl or C_{3-8} cycloalkyl optionally substituted with OH, CN or methoxy; C_{1-8} alkoxy, C_{1-4} alkyloxyalkyl, C_{1-8} alkylthio, C_{1-4} alkylthioalkyl, C_{1-8} dialkylamino, C_{1-4} dialkylaminoalkyl, CO_2R_5 where R_5 is C_{1-4} alkyl or C_{1-4} alkenyl optionally substituted with carbocyclyl or heterocyclyl; aryl or heterocyclyl connected to the pyrazole in any position that makes a stable bond, optionally substituted with halogen, C_{1-4} alkyl, C_{1-4} alkenyl, CN, Me_2N, CO_2Me, OMe, aryl, heterocyclyl or R_5.

R_2 is H, halogen, or methyl.

L is -NHC(O)-, -NHC(O)O-, -NHC(O)C(O)-, -NHC(S)-, -NH-, -NHC(O)NH, NHC(S)NH, $NHCH_2$, -NHCH(R_6)- , where R_6 is H, CN, C_{1-6} alkyl, C_{1-6} alkyloxyalkyl C_{1-6} alkythioalkyl, C_{1-6} alkylsulfinylalkyl, C_{1-6} alkysulfonylalkyl, C_{3-6} cycloalkyl, or heterocyclyl or aryl optionally substituted with a halogen, C_{1-4} alkyl, CN, Me_2N, CO_2Me or OMe, or -NHC(R_6)-lower alkyl.

R_4 is C_{1-8} alkyl, C_{1-8} alkyloxy, C_{1-8} alkylthio, C_{1-8} alkylamino, C_{1-4} alkoxyalkyl, C_{1-4} alkylthioalkyl, C_{1-4} alkylaminoalkyl C_{1-4} dialkylaminoalkyl, carbocyclyl or heterocyclyl, optionally substituted with one or more halogen, -CN, $-NO_2$, SO_2NH_2, or R_7 where R_7 is

phenyl, heterocyclyl, C_{3-6} cycloalkyl, C_{1-6} alkyl, C_{2-6} alkenyl, C_{1-6} alkyloxyalkyl, C_{1-6} alkylthioalkyl, C_{1-6} alkylsulfinylalkyl, C_{1-6} alkylsulfonylalkyl or C_{2-6} alkynyl, optionally substituted with halogen, OH, alkyloxy, CN, COO-lower alkyl, -CONH-lower alkyl, -CON(lower alkyl)$_2$, dialkylamino, phenyl or heterocycyl, CO_2R_7, $-N(R_7)_2$, $-NH(R_7)$, $-C(O)R_7$, $-OR^7$, $S(O)_nR_7$ where n is 0, 1 or 2, $-SO_2NHR_7$, $-SO_2N(R_7)_2$.

with the proviso that compounds of Formula I in which L is -NHC(O)-, R_4 is Me, R_2 is H and R_1 is Me and R_3 is Me, Cl, methylthio, or ethoxy; L is -NHC(O)-, R_2 is H, R_4 is phenyl, R_1 is methyl and R_3 is phenyl; L is -NHC(O)-, R_2 is H, R_1 and R_3 are CF_3 and R_4 is 3,5-dimethyl-4-isoxazolyl, or 4-methyl-1, 2, 3-thiadiazol-5-yl, or 4-chlorophenyl, or 4-trifluoromethoxyphenyl; L is -NH-, R_4 is Me, R_2 is H, R_3 is 4-methylsulfonylphenyl, and R_1 is trifluoromethyl or difluoromethyl; L is -NH-, R_1 is CN, R_2 is H, R_3 is 4-methylsulfonylphenyl, and R_4 is 4-methylaminophenyl or 4-ethylaminophenyl; L is -NH-, and R_1 and R_3 are Me, R_2 is H, and R_4 is 4-methoxybenzyl or 4-nitrobenzyl; L is -NHC(O)NH-, R_1 and R_3 are CF_3, R_2 is H, and R_4 is 3,5-dichlorophenyl, 3,5-difluorophenyl, or *n*-propyl; L is -C(O)NH-, R_1, R_3 and R_4 are Me; L is $-NHCH(R_6)-$, R_1 and R_3 are Me, R_6 is CN or H, and R_4 is 4-methoxyphenyl or 4-nitrophenyl; L is -NHC(O)- or -NH-, R_2 is H, R_4 is C_{1-6}alkyl or branched alkyl, and either of R_1 or R_3 is CF_3, halogen, dimethylaminomethyl, CN, C_{1-4} alkylthio, or CO_2R_5, and the other of R_1 or R_3 is a substituted or unsubstituted phenyl or heterocyclic ring are excluded.

2. The compound as recited in Claim 1 wherein:

R_1 is straight-chained, branched or cyclo- C_{3-8} alkyl, alkenyl, or alkynyl; C_{1-3} alkyloxyalkyl, C_{1-5} alkyloxy, C_{1-3}alkylthioalkyl, C_{1-5} alkylthio, CF_3; heterocyclyl or aryl optionally substituted with halogen, C_{1-4} alkyl, CN, alkoxy or Me_2N;

R_2 is H; and

R_3 is halogen, Me, Et, CF_3, CN, cyclopropyl, vinyl, SMe, OMe, heterocyclyl or aryl optionally substituted with halogen, C_{1-4} alkyl, CN, alkoxy or Me_2N;

L is -NHC(O)-, -NH-, -NHC(O)NH, -C(O)NH, or -NHCH(R_6)-, where R_6 is H, C_{1-4} alkyl, or CN and

R_4 is C_{1-6} alkyl, C_{1-4} alkyloxyalkyl, C_{1-4} alkylthioalkyl, cyclohexyl, cyclopentyl, indanyl, indolyl, phenyl, thienyl, naphthyl, isoxazolyl or pyridyl, optionally substituted with one or more halogen, -CN, -NO_2, SO_2NH_2, or R_7 where R_7 C_{1-6} alkyl, C_{2-6} alkenyl, C_{1-6} alkyloxyalkyl, C_{1-6} alkylthioalkyl, or C_{2-6} alkynyl, optionally substituted with OH, CN, -COO-lower alkyl, -CONH-lower alkyl, -CON(lower alkyl)$_2$, dialkylamino, or heterocycyl, CO_2R_7, -$N(R_7)_2$, -$NH(R_7)$, -$C(O)R_7$, -OR_7, $S(O)_nR_7$ where n is 0, 1 or 2, -SO_2NHR_7, -$SO_2N(R_7)_2$.

3. The compound as recited in Claim 1 wherein:

R_1 is Et, *i*-Pr, *n*-Pr, *t*-Bu, cyclopentyl, CF_3, -OEt, $MeOCH_2$-, 2- or 3-tetrahydrofuranyl, 2-, 3-, or 4-pyridyl, 2-furanyl, or 2-thiazolyl;

R_2 is H;

R_3 is CN, CF_3, Cl, Me, Et, SMe, cyclopropyl, vinyl, or 2-furanyl;

L is –NHC(O)-, -NH- or –$NHCH_2$-; and

R_4 is a phenyl ring which is optionally substituted with one to three groups selected from C_{1-3}alkyl, chloro, fluoro, CF_3, OC_{1-4}alkyl, OC_{3-5}alkenyl, CO_2C_{1-2}alkyl, SMe, CN, NO_2, NMe_2 and $O(CH_2)_pR_{13}$, where p is 3 or 4 and R_{13} is CN, CO_2Me, 2-(1,3-dioxolanyl), OH, or OC_6H_5; 1- or 2-indanyl, 2-tetrahydropyranyl, or a heterocycle selected from the group consisting of 2-thienyl, 3-furanyl, 3- or 4-pyridyl, 4-isoxazolyl, 1-isoquinolinyl, 2-indolyl, 2-benzothienyl and 4-pyrazolyl, which may be optionally substituted with one to three groups selected from Cl, Br, Me, CN, CF_3, OCF_3, NO_2, or $O(CH_2)_pR_{13}$, where p is 3 or 4 and R_{13} is CN, CO_2Me, 2-(1,3-dioxolanyl), OH, or OC_6H_5; C_{5-6} alkyl, C_{5-6}cycloalkyl, or cyclohexenyl.

4. The compound as recited in Claim 1 wherein:

R_1 is *i*-Pr, CF_3, 3-pyridyl or 4-pyridyl;

R_2 is H;

R_3 is CN, CF_3, Cl, Me, SMe or Et;

L is $-NHC(O)-$, -NH- or $-NHCH_2-$; and

R_4 is a phenyl ring which is optionally substituted with $O(CH_2)_3R_{13}$, where R_{13} is CN, OH or 2-(1,3-dioxolanyl); OC_{3-4}alkyl, $O(CH_2)_4OH$, 1-pentenyl, one to three groups selected from Me, Cl, F and CN; 3-pyridyl optionally substituted in the 6-position with $O(CH_2)_2OEt$ or $O(CH_2)_3R_{13}$, where R_{13} is CN, OH or 2-(1,3-dioxolanyl); 4-pyridinyl optionally substituted with a chlorine, 2-thienyl optionally substituted with Me or Br, 3,5-dimethyl-4-isoxazolyl, 1-methyl-2-indolyl, cyclopentyl, cyclohexyl, 1-indanyl or *n*-pent-3-yl.

5. A compound selected from the group consisting of:

N-[4-(5-Ethyl-3-pyridin-3-yl-pyrazol-1-yl)phenyl]pyridine-3-carboxamide;

(2-Chloro-6-fluorobenzyl)-[4-(5-ethyl-3-pyridin-3-yl-pyrazol-1-yl)phenyl]amine;

(2-Methylbenzyl)-[4-(5-ethyl-3-pyridin-3-yl-pyrazol-1-yl)phenyl]amine;

[6-(3-Cyanopropoxy)pyridin-3-ylmethyl]-[4-(5-cyano-3-pyridin-3-yl- pyrazol-1-yl)phenyl]amine;

[6-(3-[1,3]Dioxolan-2-ylpropoxy)pyridin-3-ylmethyl]-[4-(5-cyano-3-pyridin-3-yl- pyrazol-1-yl)phenyl]amine;

N-[4-(5-Ethyl-3-pyridin-3-yl-pyrazol-1-yl)phenyl]-1-methylindole-2-carboxamide;

(2-Chloro-6-fluorobenzyl)-[4-(5-cyano-3-pyridin-3-yl-pyrazol-1-yl)phenyl]amine;

[4-(5-Cyano-3-pyridin-3-yl-pyrazol-1-yl)phenyl]-(2,6-dimethylbenzyl)-amine;

(2-Chloro-6-methylbenzyl)-[4-(5-cyano-3-pyridin-3-yl-pyrazol-1-yl)phenyl]amine;

[4-(5-Cyano-3-pyridin-3-yl-pyrazol-1-yl)phenyl]-(2-indanylmethyl)amine;

[4-(5-Ethyl-3-pyridin-3-yl-pyrazol-1-yl)phenyl]-(2-indanylmethyl)amine;

[4-(5-Ethyl-3-pyridin-3-yl-pyrazol-1-yl)phenyl]- (2-fluoro-6-methylbenzyl)amine;

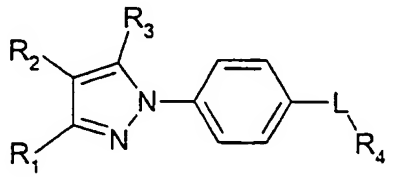
4-(3-Cyanopropoxy)-N-[4-(5-cyano-3-pyridin-3-yl-pyrazol-1-yl)phenyl]benzamide;

N-[4-(5-cyano-3-pyridin-3-yl-pyrazol-1-yl)phenyl]-4-(3-[1,3]dioxolan-2-yl-propoxy)benzamide;

[4-(3-Cyanopropoxy)benzyl]-[4-(5-ethyl-3-pyridin-3-yl-pyrazol-1-yl)phenyl]amine;

[4-(3-Cyanopropoxy)benzyl]-[4-(5-cyano-3-pyridin-3-yl-pyrazol-1-yl)phenyl]amine;

6. A method of treating an inflammatory disease which comprises administering to a patient in need of such treatment a therapeutically effective amount of a compound of formula I



wherein:

R_1 and R_3 are the same or different and each is CF_3, halogen, CN, C_{1-8} alkyl or branched alkyl or C_{1-8} alkenyl or branched alkenyl or C_{3-8} cycloalkyl optionally substituted with OH, CN or methoxy; C_{1-8} alkoxy, C_{1-4} alkyloxyalkyl, C_{1-8} alkylthio, C_{1-4} alkylthioalkyl, C_{1-8} dialkylamino,

C_{1-4} dialkylaminoalkyl, CO_2R_5 where R_5 is C_{1-4} alkyl or C_{1-4} alkenyl optionally substituted with carbocyclyl or heterocyclyl; aryl or heterocyclyl connected to the pyrazole in any

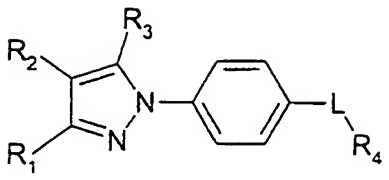
position that makes a stable bond, optionally substituted with halogen, C_{1-4} alkyl, C_{1-4} alkenyl, CN, Me_2N, CO_2Me, OMe, aryl, heterocyclyl or R_5.

R_2 is H, halogen, or methyl.

L is -NHC(O)-, -NHC(O)O-, -NHC(O)C(O)-, -NHC(S)-, -NH-, -NHC(O)NH, NHC(S)NH, $NHCH_2$, -NHCH(R_6)- , where R_6 is H, CN, C_{1-6} alkyl, C_{1-6} alkyloxyalkyl C_{1-6} alkythioalkyl, C_{1-6} alkylsulfinylalkyl, C_{1-6} alkysulfonylalkyl, C_{3-6} cycloalkyl, or heterocyclyl or aryl optionally substituted with a halogen, C_{1-4} alkyl, CN, Me_2N, CO_2Me or OMe, or -NHC(R_6)-lower alkyl.

R_4 is C_{1-8} alkyl, C_{1-8} alkyloxy, C_{1-8} alkylthio, C_{1-8} alkylamino, C_{1-4} alkoxyalkyl, C_{1-4} alkylthioalkyl, C_{1-4} alkylaminoalkyl C_{1-4} dialkylaminoalkyl, carbocyclyl or heterocyclyl, optionally substituted with one or more halogen, -CN, $-NO_2$, SO_2NH_2, or R_7 where R_7 is phenyl, heterocyclyl, C_{3-6} cycloalkyl, C_{1-6} alkyl, C_{2-6} alkenyl, C_{1-6} alkyloxyalkyl, C_{1-6} alkylthioalkyl, C_{1-6} alkylsulfinylalkyl, C_{1-6} alkylsulfonylalkyl or C_{2-6} alkynyl, optionally substituted with halogen, OH, alkyloxy, CN, COO-lower alkyl, -CONH-lower alkyl, -CON(lower alkyl)$_2$, dialkylamino, phenyl or heterocycyl, CO_2R_7, -N(R_7)$_2$, -NH(R_7), -C(O)R_7, -OR^7, S(O)$_n$$R_7$ where n is 0, 1 or 2, -SO_2NHR_7, -$SO_2N(R_7)_2$.

7. A method of treating an autoimmune disease which comprises administering to a patient in need of such treatment a therapeutically effective amount of a compound of formula I



wherein:

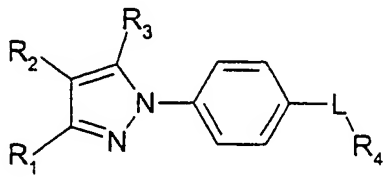
R_1 and R_3 are the same or different and each is CF_3, halogen, CN, C_{1-8} alkyl or branched alkyl or C_{1-8} alkenyl or branched alkenyl or C_{3-8} cycloalkyl optionally substituted with OH, CN or methoxy; C_{1-8} alkoxy, C_{1-4} alkyloxyalkyl, C_{1-8} alkylthio, C_{1-4} alkylthioalkyl, C_{1-8} dialkylamino, C_{1-4} dialkylaminoalkyl, CO_2R_5 where R_5 is C_{1-4} alkyl or C_{1-4} alkenyl optionally substituted with carbocyclyl or heterocyclyl; aryl or heterocyclyl connected to the pyrazole in any position that makes a stable bond, optionally substituted with halogen, C_{1-4} alkyl, C_{1-4} alkenyl, CN, Me_2N, CO_2Me, OMe, aryl, heterocyclyl or R_5.

R_2 is H, halogen, or methyl.

L is -NHC(O)-, -NHC(O)O-, -NHC(O)C(O)-, -NHC(S)-, -NH-, -NHC(O)NH, NHC(S)NH, $NHCH_2$, -NHCH(R_6)- , where R_6 is H, CN, C_{1-6} alkyl, C_{1-6} alkyloxyalkyl C_{1-6} alkythioalkyl, C_{1-6} alkylsulfinylalkyl, C_{1-6} alkysulfonylalkyl, C_{3-6} cycloalkyl, or heterocyclyl or aryl optionally substituted with a halogen, C_{1-4} alkyl, CN, Me_2N, CO_2Me or OMe, or -NHC(R_6)-lower alkyl.

R_4 is C_{1-8} alkyl, C_{1-8} alkyloxy, C_{1-8} alkylthio, C_{1-8} alkylamino, C_{1-4} alkoxyalkyl, C_{1-4} alkylthioalkyl, C_{1-4} alkylaminoalkyl C_{1-4} dialkylaminoalkyl, carbocyclyl or heterocyclyl, optionally substituted with one or more halogen, -CN, $-NO_2$, SO_2NH_2, or R_7 where R_7 is phenyl, heterocyclyl, C_{3-6} cycloalkyl, C_{1-6} alkyl, C_{2-6} alkenyl, C_{1-6} alkyloxyalkyl, C_{1-6} alkylthioalkyl, C_{1-6} alkylsulfinylalkyl, C_{1-6} alkylsulfonylalkyl or C_{2-6} alkynyl, optionally substituted with halogen, OH, alkyloxy, CN, COO-lower alkyl, -CONH-lower alkyl, -CON(lower alkyl)$_2$, dialkylamino, phenyl or heterocycyl, CO_2R_7, $-N(R_7)_2$, $-NH(R_7)$, $-C(O)R_7$, $-OR^7$, $S(O)_nR_7$ where n is 0, 1 or 2, $-SO_2NHR_7$, $-SO_2N(R_7)_2$.

8. A method of treating a disease in which excessive production of IL-2 is a contributing factor, which comprises administering to a patient in need of such treatment a therapeutically effective amount of a compound of formula I



wherein:

R_1 and R_3 are the same or different and each is CF_3, halogen, CN, C_{1-8} alkyl or branched alkyl or C_{1-8} alkenyl or branched alkenyl or C_{3-8} cycloalkyl optionally substituted with OH, CN or methoxy; C_{1-8} alkoxy, C_{1-4} alkyloxyalkyl, C_{1-8} alkylthio, C_{1-4} alkylthioalkyl, C_{1-8} dialkylamino, C_{1-4} dialkylaminoalkyl, CO_2R_5 where R_5 is C_{1-4} alkyl or C_{1-4} alkenyl optionally substituted with carbocyclyl or heterocyclyl; aryl or heterocyclyl connected to the pyrazole in any position that makes a stable bond, optionally substituted with halogen, C_{1-4} alkyl, C_{1-4} alkenyl, CN, Me_2N, CO_2Me, OMe, aryl, heterocyclyl or R_5.

R_2 is H, halogen, or methyl.

L is -NHC(O)-, -NHC(O)O-, -NHC(O)C(O)-, -NHC(S)-, -NH-, -NHC(O)NH, NHC(S)NH, $NHCH_2$, -NHCH(R_6)- , where R_6 is H, CN, C_{1-6} alkyl, C_{1-6} alkyloxyalkyl C_{1-6} alkythioalkyl, C_{1-6} alkylsulfinylalkyl, C_{1-6} alkysulfonylalkyl, C_{3-6} cycloalkyl, or heterocyclyl or aryl optionally substituted with a halogen, C_{1-4} alkyl, CN, Me_2N, CO_2Me or OMe, or -NHC(R_6)-lower alkyl.

R_4 is C_{1-8} alkyl, C_{1-8} alkyloxy, C_{1-8} alkylthio, C_{1-8} alkylamino, C_{1-4} alkoxyalkyl, C_{1-4} alkylthioalkyl, C_{1-4} alkylaminoalkyl, C_{1-4} dialkylaminoalkyl, carbocyclyl or heterocyclyl, optionally substituted with one or more halogen, -CN, $-NO_2$, SO_2NH_2, or R_7 where R_7 is phenyl, heterocyclyl, C_{3-6} cycloalkyl, C_{1-6} alkyl, C_{2-6} alkenyl, C_{1-6} alkyloxyalkyl, C_{1-6} alkylthioalkyl, C_{1-6} alkylsulfinylalkyl, C_{1-6} alkylsulfonylalkyl or C_{2-6} alkynyl, optionally substituted with halogen, OH, alkyloxy, CN, COO-lower alkyl, -CONH-lower alkyl, -

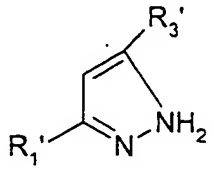
CON(lower alkyl)$_2$, dialkylamino, phenyl or heterocycyl, CO_2R_7, $-N(R_7)_2$, $-NH(R_7)$, $-C(O)R_7$, $-OR^7$, $S(O)_nR_7$ where n is 0, 1 or 2, $-SO_2NHR_7$, $-SO_2N(R_7)_2$.

9. A pharmaceutical composition comprising a compound according to claim 1 and a pharmaceutically acceptable carrier or adjuvant.

10. 1-(4-Nitrophenyl)-3-(pyridin-3-yl)-1H-pyrazole-5-carbonitrile.

11. 1-(4-Nitrophenyl)-3-(pyridin-3-yl)-5-ethyl-H-pyrazole.

12. A method of making a pyrazole intermediate useful in preparing pharmaceutical compounds which comprises the steps of reacting a 3,5-disubstituted-1H-pyrazole

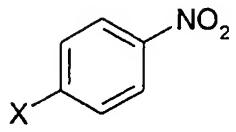


wherein

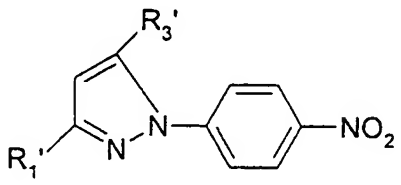
R_1' is alkylcarbonyl or an ether $CH(R_a)OR_b$, where R_a is hydrogen or methyl and R_b is a suitable protecting group, and

R_3' is C_{1-4}alkyl,

with a nitrobenzene substituted in the 4-position with a leaving group X



in a solvent with a base at about 75°C for about one hour to yield 1-(4-nitrophenyl)-3,5-disubstituted –1H-pyrazole as the dominant product



and isomeric 1-(4-nitrophenyl)-3,5-disubstituted-1H-pyrazole as the minor product.

13. A method of preparing 3-alkyl-1-(4-aminophenyl)-5-substituted-1H-pyrazole useful as an intermediate in preparing pharmaceutical compounds which comprises the steps of:

(a) reacting 1-(4-nitrophenyl)-3-[1-(tetrahydropyran-2-yloxy)alkyl]-5-substituted-1H-pyrazole with an acid in a solvent to yield the alcohol 3-(1-hydroxyalkyl)-1-(4-nitrophenyl)-5-substituted-1H-pyrazole,

(b) treating such alcohol with an oxidizing agent to yield the ketone 3-alkanoyl-1-(4-nitrophenyl)-5-substituted-1H-pyrazole;

(c) using a Wittig reaction with a phosphorous ylide derived from methyl-triphenylphosphonium bromide to convert the ketone to the olefin 3-(1-alkylvinyl)-1-(4-nitrophenyl)-5-substituted-1H-pyrazole; and

(d) reacting the olefin under reducing conditions to yield 3-alkyl-1-(4-amino-phenyl)-5-substittued-1H-pyrazole.

14. A method of preparing a 5-cyanopyrazole useful as an intermediate in preparing pharmaceutical compounds which comprises the steps of

(a) reacting 3-acetylpyridine with diethyl oxalate in a suitable solvent in the presence of a base to produce 2,4-dioxo-4-pyridin-3-yl butyric acid ethyl ester;

(b) condensing such ester with hydrazine in a suitable solvent to form a 3,5-di-substituted pyrazole, 3-(pyridin-3-yl)-1H-pyrazole-5-carboxylic acid ethyl ester,

(c) reacting such 3,5-disubstituted pyrazole ethyl ester with a suitable base in a suitable solvent to form an anion at the 1-positon of the pyrazole;

(d) reacting the resulting pyrazole with the anion at the 1-positon with fluoronitrobenzene to produce a 1-nitrophenyl-3,5-disubstituted pyrazole ethyl ester, 1-(4-nitrophenyl)-3-(pyridin-3-yl)-1H-pyrazole-5-carboxylic acid ethyl ester;

(e) hydrolyzing the 1-nitrophenyl-3,5-disubstituted pyrazole ethyl ester with a suitable base in a suitable solvent to form a 1-nitrophenyl-3,5-disubstituted pyrazole carboxylic acid, 1-(4-nitrophenyl)-3-(pyridin-3-yl)-1H-pyrazole-5-carboxylic acid;

(f) reacting the 1-nitrophenyl-3,5-disubstituted pyrazole carboxylic acid with a suitable chloroformate in the presence of a suitable base followed by addition of ammonium hydroxide to form a 1-nitrophenyl-3,5-disubstited pyrazole carboxamide, 1-(4-nitrophenyl)-3-(pyridin-3-yl)-1H-pyrazole-5-carboxamide; and

(g) dehydrating the resulting carboxamide with a suitable dehydrating agent in a suitable solvent to provide a 1-nitrophenyl-3,5-disubstituted pyrazole carbonitrile, 1-(4-nitrophenyl)-3-(pyridn-3-yl)-1H-pyrazole-5-carbonitrile.

INTERNATIONAL SEARCH REPORT

Intern ıal Application No
PCT/US 99/12295

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D231/14 C07D401/04 A61K31/415 A61K31/42 A61K31/505
A61K31/50 A61K31/47 A61K31/44 C07D413/04 C07D413/12
C07D401/12 C07D405/14 C07D401/14 C07D403/12 C07D405/12

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5 242 940 A (WACHTER MICHAEL P ET AL) 7 September 1993 (1993-09-07) abstract; claims column 6; figure 1 column 15 -column 16; examples	1,6-9
A	EP 0 242 322 A (SANDOZ AG ;SANDOZ AG (DE); SANDOZ AG (AT)) 21 October 1987 (1987-10-21) abstract; claims page 8 -page 18; examples	1

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
12 October 1999	27. 10. 99

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Paisdor, B

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INTERNATIONAL SEARCH REPORT

Interr ial Application No
PCT/US 99/12295

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D409/12 C07D409/14 C07D495/04 //(C07D495/04,333:00, 333:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	PATEL, HIMATKUMAR V. ET AL: "Synthesis of substituted 6-(3',5'-dimethyl-1H-pyrazol-1-yl)quinolines and evaluation of their biological activities" INDIAN J. CHEM., SECT. B (1990), 29B(9), 836-42 , XP002118580 the whole document ---	1
A	EP 0 418 845 A (FUJISAWA PHARMACEUTICAL CO) 27 March 1991 (1991-03-27) cited in the application abstract; claims 1,11 page 27 -page 55; examples ---	1,6-9
	-/--	

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
12 October 1999	

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Paisdor, B

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Intern ıal Application No
PCT/US 99/12295

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	FERNANDES, P. S. ET AL: "Synthesis and nucleophilic addition to conjugated imines of 1-(p-Aminophenyl)-3,5-dimethylpyrazole" J. INDIAN CHEM. SOC. (1977), 54(9), 923-4 , XP002118581 cited in the application the whole document	1
P,A	WO 99 19303 A (YAMANOUCHI PHARMACEUTICAL CO., LTD., JAPAN) 22 April 1999 (1999-04-22) abstract page 35 -page 36; table 2 page 40; table 4	1,6-9

1

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Ir. .ational application No.
PCT/US 99/ 12295

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 6-8
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 6-8 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 99/12295

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5242940 A	07-09-1993	NONE	
EP 0242322 A	21-10-1987	AT 83477 T	15-01-1993
		AU 602884 B	01-11-1990
		AU 7004887 A	24-09-1987
		BR 8701205 A	12-01-1988
		CN 1017397 B	15-07-1992
		DE 3783070 A	28-01-1993
		DK 134587 A	19-09-1987
		EG 18296 A	30-10-1992
		ES 2053579 T	01-08-1994
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